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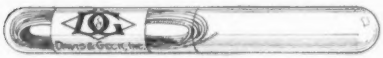

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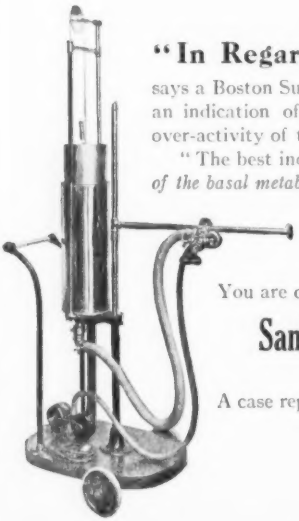

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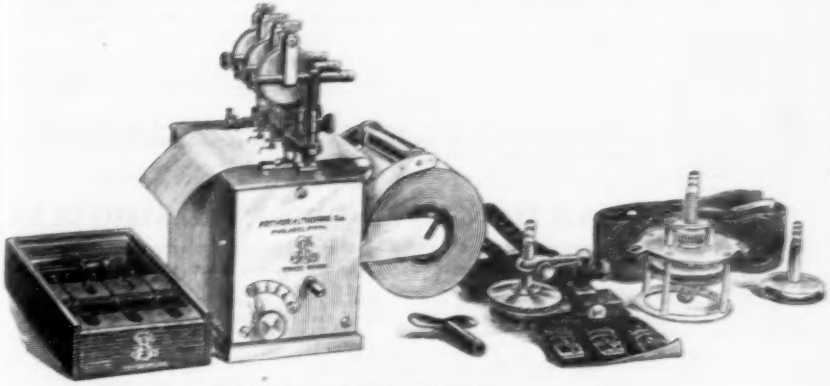

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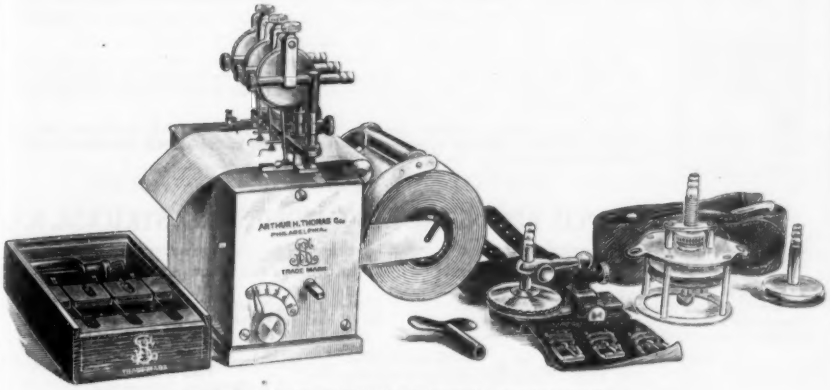

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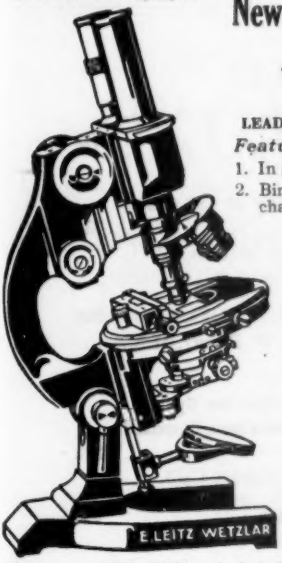

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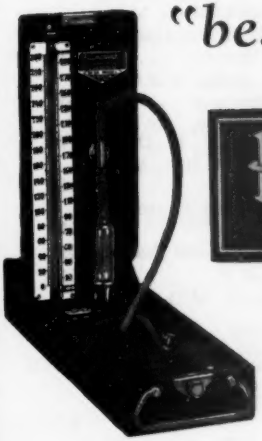

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MARCH, 1924

ORIGINAL ARTICLES.

THE CLINICAL SIGNIFICANCE OF THE PATHOLOGICAL CHANGES IN HODGKIN'S DISEASE.

By Douglas Symmers, M.D.,

DIRECTOR OF LABORATORIES, BELLEVUE AND ALLIED HOSPITALS, NEW YORK.

(From the Pathological Laboratories of Bellevue Hospital.)

(*Continued from February*, 1924)

Group II. Involvement of the Lymphoid System and Destruction of Tissues Beyond It. Case XI. *Destruction of Muscle Tissues.*—P. B., aged forty years, was admitted to Bellevue Hospital, August 1, 1921, and died January 10, 1922. The patient stated that three years previous to admission he had noticed enlarged nodes in the left axillary region. Eight months before admission he began to suffer from pain in the back, radiating to the hips and knees. Two months before admission he noticed gradual swelling of the tissues in the region of the left anterior chest wall and left axilla, attended by painless swelling of the corresponding arm and later by swelling of the legs and scrotum. Before coming to Bellevue Hospital he had been a patient in the Brooklyn Hospital, where, he stated, that a large quantity of fluid had been removed from the left chest. Dr. James Denton, at that time pathologist to the Brooklyn Hospital, removed a portion of tissue from the region of the left pectoralis major muscle. Upon microscopical examination this tissue presented the histological characteristics of Hodgkin's disease.

At the time of admission to Bellevue Hospital physical examination revealed slight enlargement of the cervical lymph nodes on

both sides and in the left supraclavicular fossa and left axilla. There was immense swelling of the left anterior chest wall, and the respiratory excursions on this side were limited. The percussion note over this area was flat, the voice sounds harsh, with fremitus absent. The left upper arm and the left thigh and both feet and ankles were edematous. The spleen was not palpable. The blood revealed hemoglobin, 65 per cent; red blood cells, 4,200,000; leukocytes, 17,500, of which there were 80 per cent polymorphonuclear neutrophiles, 9 per cent lymphocytes, 3 per cent mononuclear cells and 2 per cent transitional cells. On December 18 a quantity of thick pus was evacuated from the left chest, and on January 5 thoracotomy was done and a collection of pus was removed from the left lower part of the pleural cavity and the cavity drained.

Duration of symptoms: Three years and five months.

Autopsy Findings. Hodgkin's disease with enormous enlargement of the abdominal and thoracic lymph nodes and thickening of the left pleura, penetration of the chest wall and infiltration of the intercostal and pectoral muscles on the left side; extensive replacement of the vertebræ; nodules in the spleen and pericardium.

Histology. Microscopical examination of the lymph nodes and spleen showed a fibroblastic stroma in which were innumerable lymphocytes, numbers of mononuclear giant cells, a profusion of multinuclear giant cells and a fair abundance of eosinophiles. Sections from the intercostal muscles on the left side showed numbers of cells of identical histology with those encountered in the lymph nodes. They were strewn between the muscle bundles in such manner as to push them apart or to destroy and replace them. The corresponding pleura was immensely thickened and sclerotic. The free surface was covered by a thin layer of degenerate polymorphonuclear neutrophiles between which and the lung were streak-like or insular collections of lymphocytes, multinuclear and mononuclear giant cells and a few eosinophiles.

Comment. The enormous enlargement of the abdominal lymph nodes, together with the history of pain in the back radiating to the hips and knees, and the relatively slight involvement of the superficial nodes indicate that the primary manifestations of the disease were in the nodes of the abdomen, although simultaneous thoracic changes are not to be denied. The most striking feature of the case, of course, is to be found in involvement of the pleura, penetration of the chest wall and destruction of the muscle tissues covering the side of the chest. The association of Hodgkin's disease of the pleura with empyema constitutes a feature which, in my experience at least, is unique.

CASE XII.—J. R., aged fifty-five years, was admitted to Bellevue Hospital, August 8, 1921, and died on December 31 of the same

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year. The patient stated that three months before admission he noticed a dull aching sensation in the region of the angle of the right scapula. A few days later the right index finger was paralyzed and devoid of sensation. Two days after this the ring and little finger on the same side became similarly involved. In the course of the four months previous to admission the patient stated that he had lost 19 pounds in weight and that about three weeks before admission he had observed a painless lump in the right side of the neck and a slight cough.

At the time of admission physical examination revealed numerous discrete and movable nodes at the root of the neck, more especially on the right side. In the corresponding axilla there was an enlarged node and an area about 15 cm. in diameter, in which there was loss of the sensation of touch, pain and temperature, together with hypersensitiveness along the vertebral column corresponding to the margin of the scapula. The right arm was weaker than the left and atrophied. Examination of the chest showed some limitation of expansion on the right side. The heart sounds were muffled. During the four months that the patient was under observation at Bellevue Hospital enlarged nodes appeared in the left axilla and in the left groin. Blood count was 4,400,000 red cells; hemoglobin, 85 per cent; polymorphonuclear neutrophiles, 78 per cent; lymphocytes, 17 per cent; mast cells, 5 per cent.

Duration of symptoms: Approximately eight months.

Autopsy Findings. Hodgkin's disease of the cervical, axillary, inguinal, anterior mediastinal, periaortic and peripancreatic lymph nodes, with infiltration and replacement of the pectoral and psoas magnus muscles on the right side and the outer half of the pancreas; nodules in spleen; hydrothorax.

Histology. Microscopical examination of enlarged lymph nodes removed from different parts of the body showed rearrangement of the normal architecture due to the overgrowth of cells of the lymphocytic type, scattered among which were numbers of large mononuclear cells and a sprinkling of multinuclear giant cells, together with an occasional cell of the eosinophilic variety. In some of the nodes discrete areas or intercommunicating streaks of anemic necrosis were present, and in places an attempt was evident to replace these by newly formed connective tissue, with or without the presence of thin-walled bloodvessels. In lymph nodes removed from the abdomen, in addition to the changes just outlined, it was to be seen that the neighboring fat tissues were infiltrated by cells of the same sort, and that the walls of the medium-sized bloodvessels were invaded, providing a cellular mantle of voluminous proportions with compression of the lumen. The lumina of the small vessels were likewise frequently reduced because of the dense cellular infiltrate in which they were imbedded, aided in many instances, however, by heaping up of their lining endothe-

lium. Thromboses were sometimes to be seen both in the medium-sized and small vessels, the vascular lesions thus accounting for the necrotic areas. Much the same changes were to be found in the invaded muscle tissues—the muscle fibers were separated and partially or totally replaced by cells of the same type as those occurring in the lymph nodes and elsewhere. The walls of blood-vessels were infiltrated and nerve fibers were surrounded but rarely penetrated. In the spleen the nodular foci were composed of a preponderance of lymphocytes, among which were variable numbers of large mononuclear cells and an occasional multinuclear giant cell. Necroses were numerous, and at intervals the necrotic areas were partially replaced by granulation tissue. The adventitia of the abdominal aorta was infiltrated and banked by a collection of the same sort of cells, but the media and intima were free. Sections from the deep axilla showed large nerve trunks imbedded in and frequently penetrated by the same cellular composite.

Comment. This patient presented the picture of involvement of the lymph nodes of the neck, thorax, abdomen, axillæ and groins, with destruction of the muscles of the chest on the right side and of the right psoas magnus, together with invasion of the fat tissues of the abdomen and of the walls of the small bloodvessels and of the outer walls of the aorta, replacement of the outer half of the pancreas and nodular involvement of the spleen. In spite of this widespread destruction of tissues, the patient presented no clinical signs or symptoms indicative of disturbances in the chest or abdomen other than a slight cough which, incidentally, he attributed to cigarettes. It is interesting to observe that, clinically, the case was marked by progressive but not extensive loss in weight and by the symptoms of pressure neuritis of the right arm.

CASE XIII.—The patient, T. B., aged forty-seven years, was admitted to Bellevue Hospital, November 7, 1913, and died on January 15, 1914. The patient stated that nine months previous to admission she noticed a growth the size of a pea at the side of the nose. A month later the growth was removed in another hospital, together with the nodes of the neck.

On admission to Bellevue Hospital physical examination showed enlarged nodes in front of the right ear and in both submaxillary regions, together with numerous smaller ones in the left posterior cervical triangle, a large mass in the right axilla and nodules on the inner side of both arms and forearms, in both inguinal regions and in the left thigh. The tonsils were enlarged. Red blood cells numbered 4,912,000; white cells, 6600; polymorphonuclear neutrophiles, 66 per cent; lymphocytes, 20 per cent; large mononuclears, 10 per cent; transitionals, 4 per cent.

Duration of symptoms: Eleven months.

Autopsy Findings. Hodgkin's disease, with predominant enlargement of the peribronchial and abdominal lymph nodes; moderate enlargement of the lymph nodes of the neck and groin; multiple nodules in lungs, liver and bone-marrow of right femur; hyperplasia of both tonsils; multiple nodules beneath the skin of the trunk, arms and the lower half of the left leg; infiltration of the muscles and tendon sheaths of the right forearm directly continuous with the nodules beneath the skin of the part.

Histology. The lymph nodes revealed a fibroblastic reticulum lodged in which were innumerable cells of the lymphocytic and plasma type, eosinophiles and eosinophilic myelocytes, large mononuclear cells and a liberal sprinkling of multinuclear giant cells. Sections prepared from the bone-marrow of the ribs which, grossly, was abundant and reddish, but otherwise unchanged as far as the unaided eye could determine, revealed, on microscopical examination, changes not to be distinguished from those in the lymph nodes, including conspicuous numbers of multinuclear giant cells. The latter were of two sorts: One was a large cell with lobulated or overlapping nuclei and smooth, faintly acidophilic cytoplasm, corresponding morphologically to the myeloplaques of the normal bone-marrow; the other was a cell of slightly smaller size, with smooth, slightly basophilic cytoplasm and a hyperchromatic nucleus of variable shape—angulated or jagged, square, roughly rectangular, ovoid or otherwise atypical. This variety of giant cell, as far as I am aware, is without a prototype in the normal marrow; I have seen it in the marrow in conditions other than Hodgkin's disease, notably in syphilitic anemias of the pernicious type, but never in normal circumstances. In the case under discussion it occurred in the marrow of the ribs with noticeable frequency, and on comparing it with the giant cells encountered in microscopical preparations of the lymph nodes, lungs and tonsils from the same body it became apparent that the latter structures contained an identical variety of giant cell in numbers—a fact which tends to justify the conclusion that it found lodgment in these places as a result of discharge from the marrow by the process of embolism. Microscopical examination of the nodules in the lung revealed an histology practically the same as that of the lymph nodes, as did the nodules in the liver and the enlarged tonsils. In the skin the nodular masses were composed of vast numbers of cells of the lymphocytic type, among which were fairly numerous large mononuclear cells and, rarely, a multinuclear giant cell. Eosinophiles were not detected. The cellular infiltrate pushed its way upward to the epithelial stratum, but never beyond it, so that ulceration did not occur, and in a downward direction it separated collogen fibrils and surrounded and invaded the sweat and sebaceous glands. Microscopical examination of the muscle structures of the forearm showed the presence of a richly cellular

growth, presenting essentially the same histological characteristics as the lymph nodes, lung, etc.

Comment. This case merits remark in that the spleen was normal in size and otherwise intact. At the same time there were nodular formations in the lungs, liver and skin with infiltration and destruction of the muscles and tendon sheaths of the right forearm. The giant cells in the bone-marrow were of two sorts, typical and atypical, and morphologically indistinguishable forms were found in the lymph nodes, lungs and liver. It appears, therefore, that in the latter situations they were most probably derived from the bone-marrow by the process of embolism.

CASE XIV. **Predominant Enlargement of the Thymus in Hodgkin's Disease.**—J. E., female, aged thirty-two years, was admitted to Bellevue Hospital, May 1, 1917, and died June 17, 1917. She complained of "asthmatic" attacks of two years' duration. In the past year difficulty in breathing had increased to such an extent that she was unable to lie down night or day.

At the time of admission orthopnea was distressing and both upper extremities and the anterior chest wall were edematous. Over the right side of the chest anteriorly the percussion note was flat and expiration was high-pitched and hissing, although not frankly bronchial, and the voice sounds were high-pitched and increased in quality. The spleen was not felt. The edge of the liver was palpable about 5 cm. below the right costal slope, and there were signs of fluid in the left chest. During the seven weeks that the patient remained in the hospital the left chest was tapped five times and on each occasion from 1000 to 1500 cc of fluid were removed. The roentgen-ray report was to the effect that there was a large area of diminished illumination in the right pulmonic field, which was interpreted as due to a tumor in the anterior mediastinum. Red cells numbered 2,400,000; leukocytes, 11,000, of which 80 per cent were polymorphonuclear neutrophiles. Wassermann reaction was negative.

Duration of symptoms: Two years and seven weeks.

Autopsy Findings. The anterior chest wall was edematous. On opening the body a growth was apparent in the region normally occupied by the thymus. The growth measured 25 cm. in length and 18 cm. in thickness and was firm in consistence. It presented a whitish or faintly cream-colored substance and extended downward in such manner as to obliterate the upper part of the right pleural cavity and to invade and replace almost the whole of the two upper lobes of the right lung. The lower lobe of the lung was not involved. Scattered through the substance of both lungs were numbers of large and small, circumscribed nodules made up of tissue of identical appearance with that in the main growth. The peribronchial nodes were greatly enlarged, as were those

lying at the sides of the esophagus. The cervical and abdominal nodes were unchanged. The left pleura enclosed about 2000 cc of clear yellow fluid. The spleen was slightly enlarged, but was not nodular.

Histology. Microscopical examination of the growth in the thymic region showed a connective-tissue reticulum supporting great numbers of lymphoid cells, among which were prominent numbers of large mononuclear cells and an occasional multinuclear giant cell of the myeloid type. These giant cells exhibited a tendency to arrange themselves focally. Microscopical examination of the peribronchial lymph nodes revealed large collections of lymphocytes, among which were mononuclear and multinuclear giant cells, the islands being separated by rather coarse bands of mature connective tissue. In places these islands were permeated and partially or completely replaced by a dense, pinkish staining, poorly nucleated, hyaline reticulum, such as has been described elsewhere in this paper as a local attempt at healing. The nodules in the lung were made up almost exclusively of lymphoid cells, but among them were disclosed a few mononuclear giant cells and, rarely, a multinuclear cell of the myeloid type. Moderate numbers of eosinophiles were to be seen, usually at the periphery of the lymphoid collections. The spleen and liver were microscopically well preserved.

Comment. This is an example of Hodgkin's disease of the thymus body. I know of only 4 similar cases—one described by Yamasaki, a second by Chiari, a third by myself and a fourth by Lyon.

In Yamasaki's case[11] a woman, aged thirty-two years, presented a hugh mass in the anterior mediastinum that imitated the normal shape of the thymus. It covered the precordium and penetrated the parietal pericardium at several points. The growth invaded the pleura of the right lung and the substance of the lung itself. The sternum was eroded by direct contact and the walls of the left innominate vein and of the superior vena cava were infiltrated. The lymph nodes in the neck and in the region of the stomach were enlarged, the former appearing six weeks before death.

In Chiari's case[12] the subject was a woman, aged twenty-three years. At necropsy a mass was present in the anterior mediastinum and was described as approximating the size of a child's head. The growth was continuous with nodular masses which extended into the neck on both sides as far as the level of the thyroid cartilage, and with knob-like projections in the parietal pericardium on the right side. The trachea and larger bronchi were surrounded by nodular growths. In one of the larger bronchi the lumen was compressed and the walls were invaded; the mucosa appeared elevated, but otherwise intact. The esophagus was laterally displaced. Whitish nodules were imbedded in the pleura on the right

side. The spleen was enlarged and slightly nodular, and the lymph nodes at the head of the pancreas were described as about the size of pigeons' eggs.

In Lyon's case[13] the patient was a boy, aged twenty years, who, at necropsy, presented a growth in the thymic region that measured 12 by 7½ cm. The right lung was extensively invaded and replaced. Anteriorly the growth eroded its way through the chest wall, producing a large ulcerated area in the skin. In addition there was enlargement of the thoracic and abdominal nodes. The cervical nodes were not involved. The spleen was about normal in size, but not nodular. The patient gave a history of respiratory distress over a period of about one year and four months.

My first case[14] was that of a woman, aged fifty-six years, who during life complained of cough, dyspnea and palpitation of the heart. There was edema of the neck and right chest wall and left-sided hydrothorax. At necropsy a whitish, firm, slightly lobulated growth was found in the upper anterior mediastinum, approximating the shape of the thymus and measuring 18 cm. from above downward and 11 cm. in a transverse direction. The mass projected through the superior aperture of the thorax and invaded the lower pole of the right lobe of the thyroid gland for a distance of 3 cm. In a downward direction it covered the upper part of the precordium and displaced the heart to the left. On the right side it compressed but did not invade the lung. Posteriorly it compressed the trachea and invaded its walls for a distance of 8 cm. The mucous membrane throughout this area presented a series of small projections, but no signs of ulceration. There were numbers of slightly enlarged lymph nodes in the lower part of the neck, but the abdominal nodes and the spleen were not involved.

My second case is outlined above and calls for no further comment other than that it represents an almost exact counterpart of the four just synopsized.

In all of these cases the histological changes described in the mediastinal growths, in their continuate extensions and in the more remote nodules are in complete agreement with the histology of Hodgkin's disease as observed in other cases in the lymph nodes and elsewhere.

These 5 cases, described by four independent observers, and recorded from the clinical, anatomical and histological viewpoint, unite, I think, to establish Hodgkin's disease of the thymus body as a clinical and pathological entity.

The Lymph Nodes in Hodgkin's Disease. The term "primary Hodgkin's disease" is often used as a matter of expediency to indicate the greatest degree of enlargement of the lymphoid structures as encountered anatomically and as representing, presumably, the oldest lesions. The term, however well it may fit into everyday usage, is to be avoided in that it is apt to convey a false con-

ception of the pathology of Hodgkin's disease, which has multiple foci of origin occurring at the same or approximately the same time in the lymph nodes of the same or of separate groups, and in that the nodes of one group may enlarge progressively while those of another group may recede or remain stationary, at least for a while. Nevertheless, if one bears these facts in mind it is often practicable to arrive at a reasonably safe conclusion as to the comparative age of the respective enlargements, whether of the lymph nodes proper or of such lymphoid organs as the spleen and thymus, and thus to provide a classification of working value.

The clinical arrangement outlined and followed in this paper is founded partly on these facts and partly on an arbitrary division of the lymph nodes of the body into three great groups, and on the circumstance that, in Hodgkin's disease, the individual groups react differently.

(*a*) Included in the first group are the lymph nodes of the *neck, axilla, thorax, abdomen* and *groin*. These are the nodes which carry the great share of the burden in Hodgkin's disease.

(*b*) In the second group are the *submucosal collections*, represented by the faucial and lingual tonsils and by the minute lymphoid follicles which are strewn through the submucosa of the gastro-intestinal, respiratory and urinary tracts. They constitute an accumulation of lymphoid cells that is probably equal to, if not greater than, the numerical total of the regional collections in the neck, axilla, thorax, abdomen and groin. These submucosal lymphoid structures almost invariably escape in Hodgkin's disease.

(*c*) The *auxiliary lymphoid system:* In normal circumstances the auxiliary lymphoid system is represented by follicles in the walls of the arterioles of the spleen that are interposed as minute filters between the arterial blood brought to the spleen for purification and the venous blood which the spleen transfers to the liver for further detoxication. Beyond the confines of the spleen, and with the exception of the lymphoid cells in the thymus body, the auxiliary lymphoid apparatus in normal circumstances is a negligible quantity, but in certain pathological conditions, notably in Hodgkin's disease, it assumes a place of importance. Thus, in Hodgkin's disease and, incidentally, in pseudoleukemia and enteric fever, focal or streak-like collections of lymphoid cells are to be found in the walls of the portal veins. They represent hyperplasia of pre-existing lymphoid collections which are physiologically comparable to the follicles in the arterioles of the spleen, although in normal circumstances they are numerically insignificant and are functionally dormant until awakened by the necessity for additional filtration barriers between the blood of the portal and hepatic veins—an adjunct, as it were, to the defensive mechanism represented by the intervening liver lobules. In Hodgkin's disease the initial visible changes in the liver consist in the appearance of lymphoid

cells in the walls of the portal veins. In Hodgkin's disease, also, the interstitial tissues of the kidney occasionally exhibit focal collections of lymphoid cells, always in the richly vascularized cortex, in proximity to but not in the walls of the bloodvessels. Similar foci sometimes occur in the cortical substance of the kidney in enteric fever, pernicious anemia, lymphosarcoma and pseudoleukemia. In the lungs, lying in the interstitium or in the walls of bloodvessels, collections of lymphoid cells are to be seen in various pathological conditions, and the same statement applies to the serous membranes and to the subcutaneous tissues, the bone-marrow, the interstitial tissues of the prostate, adrenal, thyroid, etc. In the thyroid they are common in exophthalmic goiter, especially in subjects of status lymphaticus. It is obvious that the follicles of the auxiliary lymphoid apparatus, although of doubtful importance in normal conditions (the spleen excepted) are susceptible of hyperplastic changes in a variety of diseases.

In Hodgkin's disease, the initial changes in the auxiliary lymphoid tissues are strictly comparable to those in the lymph nodes proper and their subsequent development, as far as it can be followed here or elsewhere, is the same. That is to say, in the auxiliary depots preliminary lymphoid hyperplasia is followed by the appearance of a connective-tissue reticulum supporting mononuclear and multinuclear giant cells with or without eosinophiles and eosinophilic myelocytes, thus completing the histological composite and bringing it into agreement with that of the larger and more ambitious lesions in other parts of the body.

In the present series, in addition to the changes in the spleen, bone-marrow and liver, the auxiliary lymphoid apparatus was concerned in 10 cases. In 1 case a solitary hyperplastic lymph node was imbedded in the submucosa of the gall-bladder and, histologically, was identical with the lymph nodes in other localities. In the same case a small nodule was present in the walls of a bronchus and, although unfortunately not submitted to microscopical examination, it was presumably of the same nature. In 3 cases nodules were present in the cortices of the kidneys and all of them showed structural alterations indistinguishable from those in the diseased lymph nodes. In 2 cases multiple nodules of characteristic histology occurred in the lungs; in another the suprarenal capsule showed microscopical foci of involvement. In 3 cases nodules were imbedded in the epicardium. In 1 of these cases there is no histological confirmation of the identity of the nodules with the lesions in other parts, although any assumption to the contrary would scarcely seem to be justified. In the other 2 cases the histology was characteristic.

Among clinicians it is a sort of tradition that Hodgkin's disease is essentially an affection of the cervical lymph nodes. This conception, however honored by repetition, is contradicted by fact.

In this series preponderating enlargement of the cervical nodes occurred once only (7 per cent). In 4 cases, or 28 per cent, the predominant enlargements occurred in the abdominal nodes, and in 6 other cases, or 43 per cent, in the nodes of the chest and abdomen in combination—a proportion of 10 to 1. In another case the liver was the most extensively involved, and in still another the spleen. In both of them the abdominal nodes were only moderately enlarged and the cervical nodes were free in 1 case, slightly enlarged in the other. In still another case the lymphoid tissues of the thymus were enormously hyperplastic and the cervical nodes were free. In other words, in 4 of the 14 cases the nodes of the neck were not involved at all (28 per cent), in 3 they were involved only to a slight extent (21 per cent) and in the remaining 6 cases they were enlarged in association with collections in the deeper parts that were proportionately far more massive.

Finally, it is a matter of anatomical interest and of clinical value that enlargement of the axillary nodes is always a direct sequence of involvement of the cervical or thoracic groups, and that inguinal adenopathy in Hodgkin's disease is sequential to involvement of the abdominal nodes. Enlargement of the axillary or inguinal nodes independently of such changes, if it exists, did not occur in this series. These facts, taken into consideration with the distribution of the lesions in the lymph nodes of the neck, thorax and abdomen, seem to substantiate the view that the provocative agent in Hodgkin's disease, whatever it may be—bacterium, filterable virus or what not—does not enter through the skin, but exclusively through mucous membranes; that it is apt to pass the first barrier of lymphoid tissues, namely, the small collections which lie in different submucosæ, without exciting any notable disturbances in them, and that it produces its greatest degree of reaction in those lymphoid structures which are situated at strategic points for purposes of filtration, namely, the lymph nodes of the neck, thorax and abdomen. In the neck, for example, enlargement of the tonsils is an infrequent prelude to disturbances in the lymph nodes of the immediate vicinity. The mediastinal nodes often attain enormous proportions without participation of the submucous lymphoid collections in the trachea and bronchi; in the abdomen the mesenteric and retroperitoneal nodes may exhibit an extraordinary degree of enlargement without changes in the solitary or agminated follicles of the intestine. In still other circumstances it appears that the provocative agent is capable of passing both the primary and secondary lines of defense; that is to say, it may filter through both the submucous follicles and the lymph nodes in the neck, thorax or abdomen, and bring about hyperplastic changes in the follicles of the spleen or in the lymphoid remains of the thymus. Moreover, Hodgkin's disease, as revealed at necropsy, not uncommonly shows a tendency to skip groups of

lymph nodes, as is shown by the combination of cervical and abdominal enlargement without participation of the nodes in the chest.

One does not have to seek far for examples of toxic lymphoid hyperplasia analogous to those encountered in Hodgkin's disease. In certain diseases of established etiology, notably tuberculosis, it is known that absorption of toxins from ulcerative lesions in the gut is capable of producing simple hyperplastic changes in the mesenteric lymph nodes without the intervention of tubercles. In a case which recently came under my observation at Bellevue Hospital, bilateral tuberculosis of the psoas magnus muscles, secondary to caseation of a vertebra, was attended by enlargement of the spleen, the organ weighing 1980 gm. and measuring 20 by 10 by 6 cm. Scattered through it were myriads of pinhead-sized yellowish foci. The retroperitoneal lymph nodes were hyperplastic to a marked degree. Microscopical examination of the spleen and of the lymph nodes revealed hyperplasia of the lymphoid follicles without a tubercle to be found in any one of numerous microscopical sections which were prepared with the object of determining this point. In typhoid fever the absorption of toxins from ulcers in the intestine is notorious as producing lymphoid hyperplasia in the mesenteric nodes, and in diphtheria simple hyperplasia of the cervical nodes is not uncommonly to be traced to absorption from the exudate in the throat.

The Liver in Hodgkin's Disease. In 10 cases of the present series (71 per cent) the liver presented foci of characteristic histology. In 8 cases nodules were visible to the naked eye, varying in size from ½ to 2 cm. Microscopical examination showed that the nodular foci arose in the periportal spaces and were initiated by hyperplasia of the lymphoid cells in the walls of the portal veins, followed by the appearance among the lymphocytes of mononuclear and multinuclear giant cells with or without the presence of eosinophiles and eosinophilic myelocytes, the whole supported in a connective-tissue reticulum, the nodules expanding in such fashion as to subject the neighboring lobules to atrophy from pressure, but never directly infiltrating them.

In one case a huge solitary mass surrounded the portal vein shortly after it entered the liver at the transverse fissure, and appeared both to the naked eye and on microscopical examination to arise in the walls of the vein and thence to expand concentrically, pushing aside the liver tissue but not invading it. In addition, innumerable foci of microscopical size and of identical histological structure were found in the periportal connective tissues.

In Case VIII the liver was greatly enlarged. There were a few enlarged lymph nodes in the abdomen, histological examination of which showed the characteristic histology of Hodgkin's disease. Ascites was abundant. The shape of the liver was preserved in

spite of the fact that its substance was replaced to an enormous degree by fibrous bands (Fig. 1). Histologically, the changes followed the same evolution as those described in the liver in the other cases, differing, however, in the almost incredible extent to which the organ was replaced by connective tissue, due to thickening of the intrahepatic portal veins, in the walls of which microscopical examination showed the histological features of Hodgkin's disease. As far as I can learn, the extent of the changes in the liver in this case constitutes a phase in the pathology of Hodgkin's disease which has not hitherto been pointed out. The larger veins in the substance of the spleen were likewise greatly thickened and in their walls were collections of lymphoid cells and numbers of atypical giant cells. The extent of the changes in the spleen, however, was insignificant as compared with those in the liver. Nevertheless, in both of these localities the histological changes of Hodgkin's disease were found most frequently and in their most highly developed state in the walls of veins; involvement of the lymph nodes, although present, was practically negligible. I assume, therefore, that there is a variety of Hodgkin's disease in which the predominant changes occur in the lymphoid collections in the walls of veins. In this particular case the greatest degree of enlargement occurred in the liver. Perhaps it is not trespassing too far to predict that future investigation will disclose a variety of splenomegaly in Hodgkin's disease in which the size of the spleen will be shown to depend on changes in its larger veins of the same sort as those here described in the veins of the liver.

The Spleen in Hodgkin's Disease. Of the 14 cases in this series, the spleen was greatly enlarged in 9 (64 per cent). The weights recorded in 8 of the cases were 450, 500, 657, 700, 750, 840, 1220 and 1300 gm., an average of 802 gm., or 652 gm. in excess of the average weight of the spleen in health. In 8 of the 9 cases of splenomegaly, characteristic histological changes were present. In the ninth case the spleen measured 15 by 9 by 5 cm., but on microscopical examination it was found to be extensively sclerotic and the histological alterations of Hodgkin's disease were not detected, having been replaced, no doubt, by the overgrowth of connective tissue. The alternative conception that the enlargement of the spleen was due to an independent process appears to be somewhat strained. In 2 other cases the histological changes in the spleen were characteristic of Hodgkin's disease, but the organ was normal in size or only slightly enlarged and was not palpable during life. In the remaining 3 cases the spleen was normal both in size and microscopically, and was likewise not palpable during life.

Destruction of Muscle Tissues. The present study emphasizes the fact that individual skeletal muscles or groups of muscles may suffer extensive destruction by invasion of tissue of the same sort as that in the lymph nodes and elsewhere. Cunningham[15] noted

similar changes in one of his cases. In one of the cases here recorded enlarged abdominal nodes were continuous with voluminous nodes in the thorax, and these, in turn, were associated with a thickened and adherent pleura on the left side and with penetration of the intercostal muscles and continuate infiltration of the muscles of the corresponding pectoral region, producing a mass on this side of the chest which in size and shape resembled a miniature ham. In a second case enlarged lymph nodes in the neck were continuous with infiltration of the pectoral muscles on the right side, covering an area only slightly smaller than that of an average adult hand, and in the abdomen enlargement of the regional lymph nodes was attended by almost complete destruction of the right psoas magnus muscle. In a third case nodules in the skin of the right forearm were attended by continuate infiltration of adjacent muscles and tendon sheaths. In all of these cases the invaded muscle tissues were subjected to microscopical examination and in all of them the histological composite of Hodgkin's disease differed in no wise from that of the lymph nodes and other tissues.

The Bone-marrow in Hodgkin's Disease. In the present series, the bone-marrow was involved in 7 cases (50 per cent). In 1 case the marrow of all the thoracic and lumbar vertebræ was completely replaced by whitish tissue of the same sort as that in the lymph nodes, the intervertebral disks and the bony casement of the vertebral bodies remaining intact. In another case the anatomical diagnosis refers to "extensive replacement of the vertebræ," but the text of the protocol makes no mention of the part of the vertebral column involved. In this case, however, microscopical examination of the marrow showed: (*a*) Replacement by tissue of identical composition with that in the lymph nodes—a reticulum with lymphocytes and mononuclear and multinuclear giant cells; (*b*) areas of granulation tissue with innumerable thin-walled blood-vessels lying in a matrix of lymphocytes, polymorphonuclear neutrophiles, eosinophiles, eosinophilic myelocytes and red cells; (*c*) hyperplastic marrow, rich in cells of the sort just enumerated plus large mononuclear and myeloid giant cells. In 5 other cases the marrow spaces were occupied to a variable extent by tissue microscopically identical with that of the diseased lymph nodes. In 2 instances microscopical examination of sections from the marrow showed, in addition, numbers of giant cells with nuclei which presented all sorts of odd shapes. Morphologically identical giant cells were found in the liver in 1 of the cases, and in the lymph nodes, lungs and tonsils in another, suggesting that the giant cells had been deposited in these localities as a result of embolism from the bone-marrow.

In short, the bone-marrow in Hodgkin's disease reacts in at least two different ways: (*a*) It may show hyperplastic changes characterized by increase in the cells normally manufactured

there; (*b*) it may be replaced by tissue of identical composition with that in the diseased lymph nodes, focally or over a wide geographical range. These two types of reaction may be encountered in the bone-marrow not only in one and the same case, but in the same microscopical field.

The Nature of Hodgkin's Disease. By some pathologists, Hodgkin's disease is regarded as an infective granuloma. All attempts thus far made to establish a causal relationship between it and different microörganisms have failed. By others it is looked on as a neoplasmic process. There is something to be said for and against both of these views. As a rule, tumors, excluding, of course, such growths as the teratomata, are dominated by a single type of cell or by variations of the same type, as in the mixed spindle- and giant-cell sarcomata. When tumors metastasize the secondary growths ordinarily present histological changes identical with or closely comparable to those of the parent growth, but instances are common in which it is difficult or impossible to correlate the structure of the primary growth with that of its metastases or with its continuate infiltrate or its recurrent growth, or even with different parts of the parent growth, the rapid reproduction of cells, together with alterations brought about by environment, combining to produce remarkable changes in their shape and arrangement. On the other hand, the histological composite in Hodgkin's disease remains essentially the same throughout all changes of environment, in which respect it resembles an inflammatory lesion of the granulomatous type. In favor of the neoplasmic nature of Hodgkin's disease, it may be advanced that the process sometimes produces continuate infiltration and destruction of tissues, as has been emphasized in the present paper. On the other hand, inflammatory diseases of established etiology often pursue an equally ravenous course, notably actinomycosis, tuberculosis and the like, and, as in Hodgkin's disease, they tend to maintain their histological individuality no matter what the environment may be. Again, it may be urged that Hodgkin's disease produces circumscribed nodular lesions in different organs and that in this respect it resembles a neoplasm, but, unfortunately for this argument, inflammatory diseases may react similarly, as witness the presence of gummata in syphilis and massive solitary tubercles in the brain, together with the occasional occurrence of elevated nodules in the liver in chronic myelogenous leukemia; and yet there is no proof that myelogenous leukemia is a neoplasmic process, although this, of course, is a theory that is sometimes discussed. The wide distribution of the lymph-node enlargements in certain cases of Hodgkin's disease and their immense size may be quoted in favor of the neoplasmic nature of the disease, but this is offset by the observation that primary disseminated tuberculosis of the lymph nodes may pursue it as a close second. Moreover,

in Hodgkin's disease the lesions in the lymph nodes and elsewhere are made up of cells of different morphology—lymphoid and plasma cells, mononuclear and multinuclear giant cells, eosinophiles and eosinophilic myelocytes—and in order to fit into the category of metastases the secondary deposits would have to reach their new abode in the form of diversified cell collections and to proliferate as such. The alternative conception is equally fantastic, namely, that a single type of cell, when transplanted, is capable of reproducing a cell complex.

Hodgkin's disease occasionally shows spontaneous attempts at healing, as exemplified by the overgrowth and hyalinization of connective tissues, sometimes to such an extent that, in a given territory, the character of the process is completely obscured. The argument that this is in favor of the inflammatory nature of the disease is countered by the fact that in malignant tumors the overgrowth of connective tissue sometimes constitutes an equally adequate attempt at healing, as shown, for example, in scirrhous carcinomata of the breast.

It seems to me that Hodgkin's disease does not provide any criteria by which it may be grouped either among the inflammatory diseases or among the neoplasms, but that, for purposes of classification, it must be included elsewhere. Pathologists have thus far found it impossible to formulate an acceptable definition of inflammation and of neoplasia, partly for the reason that there are so many diseases which partake of the nature of both. Hodgkin's disease, I believe, is to be included in this category, together with mycosis fungoides, Cohnheim's pseudoleukemia, Sternberg's leukosarcoma, Gaucher's splenomegaly, Kaposi's lymphodermia perniciosa and a number of others. If, however, there is anything to be said in favor of one argument or the other it is that Hodgkin's disease more closely approaches an inflammatory disease in that *it maintains its histological individuality throughout all changes of environment.*

The first observable histological change in the lymph nodes in Hodgkin's disease consists in hyperplasia of lymphoid cells.[16] The same statement applies to other lymphoid tissues, whether in the spleen, liver, kidney, adrenal, lung, serous membranes or elsewhere. In these localities, in the fully developed disease, the histological changes are strictly comparable to those in the lymph nodes themselves. As development proceeds the hyperplastic lymph nodes begin to lose their architectural identity, the germinal follicles disappear and the lymph cords are moulded into diffuse sheets of lymphoid cells, and at least two alien cells make their appearance to lend individuality to the microscopical picture. One of these cells is to be found in varying numbers in the lymph or blood sinuses or *lying free* among the lymphocytes or in the tissue spaces. It is a large rounded cell and is indistinguishable from the non-

granular, mononuclear cell of the normal bone-marrow. The other is larger and of identical morphology with that encountered in the normal marrow in the form of cells variously known as myeloplaxes, multinuclear myeloid giant cells, megacaryocytes and the like. In the lymph nodes, in the earlier stages of Hodgkin's disease, these myeloid giant cells *lie loose among the lymphocytes and are almost always partially or completely surrounded by a clear zone.* There is another cell which forms an important feature of the pathological-histology of Hodgkin's disease. It occurs in varying numbers in a considerable percentage of all cases—the polymorphonuclear eosinophile. In addition, there is a closely related cell which occurs in the lymph nodes in about one-third of all cases, namely, the eosinophilic myelocyte. Sometimes it is the only eosinophilic cell present; at other times it is associated with polymorphonuclear eosinophiles. In other words, *the lymph nodes and other lymphoid tissues in the fully developed Hodgkin's disease show a composite of cells, each member of which finds its prototype in the normal bone-marrow.*

In the lymph nodes of Hodgkin's disease freshly removed during life and fixed immediately in formalin or in Zenker's solution I have failed to find indications of mitotic activity in the nuclei of the lining endothelium of capillaries or lymph sinuses or other evolutionary changes in them that would account for the formation of giant cells, nor have I ever been able to trace any relationship between the giant cells and the connective tissues of the part, nor to detect any changes in the nuclei of either the mononuclear or multinuclear giant cells that appeared to me to indicate an attempt at reproduction. On several occasions, however, I have detected both mononuclear and multinuclear giant cells lying free in the lumina of capillary vessels in the enlarged lymph nodes, as if fixed in the actual process of embolism from the bone-marrow (Fig. 4). Giant cells of identical morphology with those of the normal bone-marrow have been found in film preparations of the blood in Hodgkin's disease, independently by Bunting[17] and by Minot;[18] and in 3 of 5 cases of Hodgkin's disease Bunting found increased numbers of megacaryocytes in microscopical sections of the bone-marrow. In my experience, I have sometimes found them in the marrow in increased numbers, indicating a response to increased demand from the peripheral tissues; in other cases I have estimated them as present in normal numbers; in still other instances I have been unable to find them in the bone-marrow at all or only to a negligible extent, in which circumstances it is probable that they had been exhausted as a result of repeated expulsion into the circulation. If megacaryocytes in Hodgkin's disease are discharged into the circulation in variable numbers and at irregular intervals, over a period of months or years, it follows that their numbers in the bone-marrow must vary, depending on the rate of discharge and

the capacity of the marrow to replenish the supply. Moreover, in Hodgkin's disease I have found atypical mononuclear and multinuclear giant cells in sections of the bone-marrow, together with identical atypical forms in the lymph nodes and other extramedullary tissues in one and the same case, which, I take it, is presumptive evidence of their derivation from the bone-marrow by the process of embolism. Flexner's observations on lymphotoxins and myelotoxins have shown that injection of these substances into certain animals is followed by hyperplasia of the lymphoid tissues and by increase in the non-granular mononuclear cells, the granular leukocytes and the multinuclear giant cells of the bone-marrow.[19]

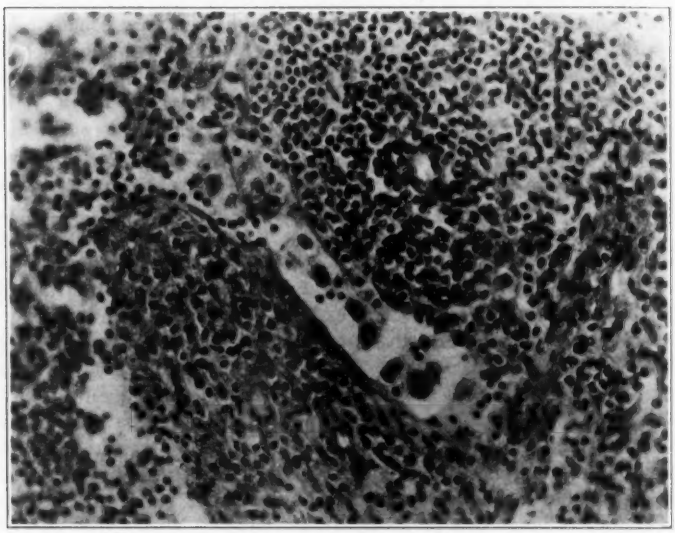

FIG. 4.—High-power photomicrograph showing mononuclear and multinuclear giant cells in the capillaries of a lymph node in Hodgkin's disease, the alien cells being derived, presumably, from the bone-marrow by the process of embolism.

Exactly similar changes occur in the same situations in Hodgkin's disease. Moreover, in chronic myelogenous leukemia the occurrence of megacaryocytes in the blood and in the spleen, liver and lymph nodes is well recognized and is commonly ascribed to embolism from the bone-marrow. If, as is sometimes claimed, the multinuclear giant cells in the lymph nodes and elsewhere in Hodgkin's disease are formed outside the bone-marrow then it may be assumed with equal reason that the corresponding cells in myelogenous leukemia are also formed beyond the bone-marrow. In these circumstances consistency demands that it be assumed that the myelocytes in the blood are manufactured outside the bone-

marrow, and, therefore, that the changes in the marrow in myelogenous leukemia are purely ornamental. I doubt if any thoughtful student of pathology would subscribe to this view. Either the megacaryocytes and myelocytes both are manufactured in the bone-marrow and are discharged into the blood, or both are products of tissue outside the marrow. Of the latter, there is no morphological proof, while the former view is supported by morphological findings and by arguments based on consecutive reasoning. That the megacaryocytes in the blood or tissues are manufactured *in situ*, and that the myelocytes in the same disease and in the same localities are derived from the bone-marrow, appears to be a still more illogical attempt to straddle an impossible situation.

I see no reason why the same argument should not be applied to Hodgkin's disease, where megacaryocytes have been identified in the blood and in the lymph nodes, liver, spleen and other tissues, together with eosinophiles and eosinophilic myelocytes; in other words, that the reaction of the bone-marrow in Hodgkin's disease and in chronic myelogenous leukemia is fundamentally the same, although the two diseases differ in the relative numbers of the cells discharged and in the reaction of the recipient tissues. In myelogenous leukemia the bone-marrow is excessively hyperplastic; myelocytes are discharged into the blood stream in enormous numbers and circulate as such; megacaryocytes are discharged in small numbers and on infrequent occasions, but nevertheless are to be found in the peripheral blood and in the bloodvessels of the deeper organs, notably in the sinusoids of the liver and in the spleen and lymph nodes. In Hodgkin's disease the bone-marrow is less richly hyperplastic; megacaryocytes are discharged in considerable numbers but at irregular and infrequent intervals. They have been found in the peripheral blood, and that they are not more commonly detected there is probably due to the fact that they circulate in small numbers and at irregular intervals. In the lymph nodes, spleen, liver and other lymphoid tissues they are to be identified in numbers—sometimes as the most prominent, although not the predominant, cell in the microscopical picture. Much the same statement applies to the large mononuclear giant cell and to the eosinophiles and eosinophilic myelocytes. In Hodgkin's disease they undoubtedly circulate, but at irregular intervals and in small numbers. Moreover, both in Hodgkin's disease and in chronic myelogenous leukemia the blood platelets have been shown to be increased in number, indicating increased activity in the marrow.

Further evidence tends to show that Hodgkin's disease and chronic myelogenous leukemia are more intimately related than is indicated by the customary text-book presentations, where it is commonly stated that in chronic myelogenous leukemia the lymph nodes do not participate at all. According to our experience at

Bellevue Hospital, this statement is erroneous. In 4 cases of myelogenous leukemia encountered at necropsy the lymph nodes in various localities were enlarged—most often in the abdomen, but occasionally in the groin and thorax, although neither in number nor in size did they begin to approach those customarily met with in Hodgkin's disease. In myelogenous leukemia and in Hodgkin's disease it appears that the provocative agent brings about changes in the lymph nodes that are qualitatively alike, but quantitatively different. In myelogenous leukemia the lymph nodes are enlarged because of simple hyperplasia of lymphoid

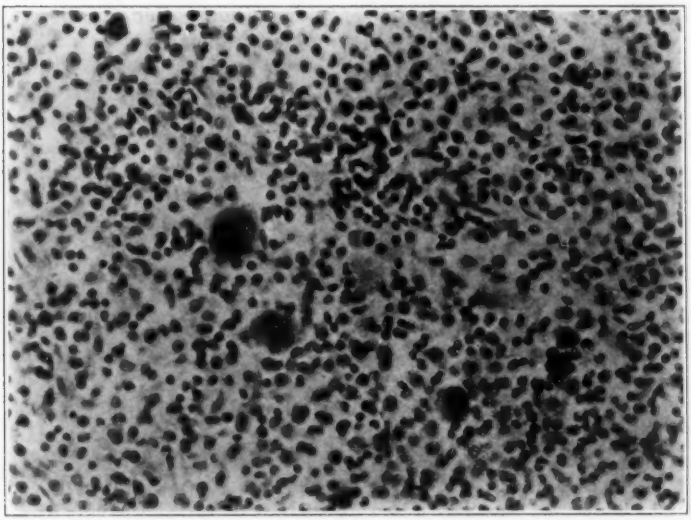

FIG. 5.—High-power photomicrograph showing mononuclear and multinuclear giant cells. From an enlarged lymph node in a case of chronic myelogenous leukemia. The histology of the lymph node is strikingly like that encountered in the same situation in Hodgkin's disease.

cells, in which respect they correspond to the smaller and more recently involved lymph nodes in Hodgkin's disease, where lymphoid hyperplasia is the predominant feature. There are instances, however, in which the lymph nodes and spleen in myelogenous leukemia might easily be mistaken, histologically, for those of Hodgkin's disease because of the presence of considerable numbers of mononuclear and multinuclear giant cells and of eosinophilic myelocytes among the hyperplastic lymphoid cells (Figs. 5 and 6). However, the histological distinction from Hodgkin's disease may be made on the ground that overgrowth of connective tissue, if it occurs, is not sufficient to obscure the architecture of the organ.

In addition, of course, the bloodvessels show vastly increased numbers of myelocytes in their lumina. In Hodgkin's disease, in the majority of cases, enlargement of the lymph nodes is excessive, but in occasional instances it does not greatly transcend that of myelogenous leukemia, as shown in several cases in this series.

It appears, therefore, that in myelogenous leukemia and Hodgkin's disease there is a certain parallelism between the reaction of the bone-marrow and of the lymph nodes and spleen which suggests that the two diseases are fundamentally related—that they are probably different quantitative responses to the same type of provocative agent.

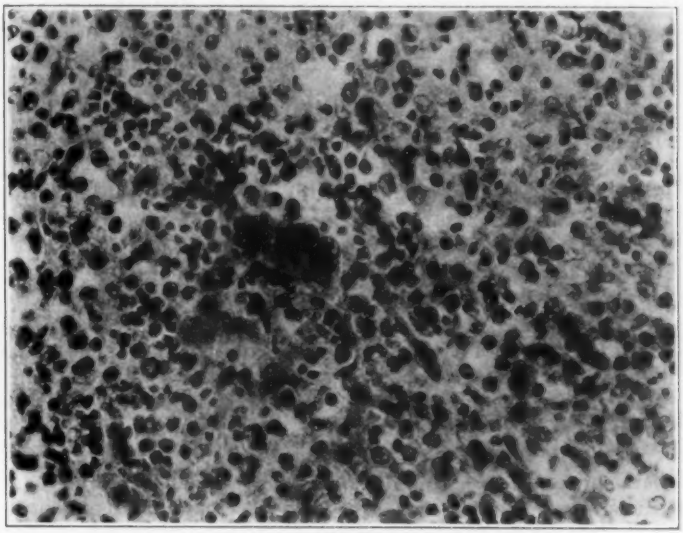

FIG. 6.—High-power photomicrograph showing multinuclear myeloid giant cells in the spleen. From a case of chronic myelogenous leukemia. Note the resemblance of the histological changes to those of Hodgkin's disease.

Symptoms and Signs, Duration, Treatment, Prognosis. *Symptoms and Signs.* Of the 14 cases in this series subjective symptoms were lacking in 5, in spite of huge lymph-node enlargements in the neck in 1, in the chest and abdomen in another and in the abdomen in the remaining 3. In another 5 cases there were complaints of pains in the abdomen or back, in association with enlarged abdominal nodes, and in 2 other cases subjective symptoms were referable to pressure on the nerve trunks of the upper extremity. In 1 instance a scalding sensation on urination was associated with pressure at the neck of the bladder. In all of the 14 cases objective signs were apparent in the form of lymph-node enlargements

in the neck, axilla or groin, emaciation, anemia, edema, changes in the skin, such as jaundice, exfoliative dermatitis and acanthosis nigricans, with or without the late appearance of such symptoms as cough and dyspnea, dependent on the pressure of enlarged lymph nodes within the thorax. The escape of fluid into various loose tissues or serous sacs was present in 10 cases (71 per cent); in the remaining 4 cases no signs of effusion were evident. Subcutaneous edema of the legs, scrotum, etc., occurred 3 times, always in company with enlargement of the intra-abdominal nodes. In 1 instance subcutaneous edema of the forearm occurred in association with invasion of the muscle tissues and tendon sheaths of the vicinity by tissue of the same sort as that encountered in the diseased lymph nodes; in a second, edema of the left pectoral region was attended by tumor-like infiltration of the muscles of the corresponding part and in a third, edema of the chest wall was present as a pressure phenomenon in Hodgkin's disease of the thymus. Involvement of the serous sacs occurred in different combinations in 10 cases, nine times as pure serous effusions and once as a purulent exudate. Ascites was noted five times, and in 4 cases was apparently due to enlargement of the intra-abdominal nodes, in the remaining case to primary involvement of the liver; bilateral hydrothorax occurred four times, twice attended by enlargement of the intrathoracic nodes and twice as a terminal event; unilateral hydrothorax was encountered twice, once accompanied by massive enlargement of the thymus. In 1 case the left pleura enclosed large collections of pus. The pleura itself was enormously thickened and in it were small composites corresponding in all histological essentials with those encountered in the same case in the lymph nodes and elsewhere—an instance of secondary involvement of a pleural membrane presenting the characteristic histology of Hodgkin's disease, and the only case in this series attended by empyema, the other effusions representing serous transudates due to interference with the venous return.

Duration. The rarity of subjective symptoms in Hodgkin's disease is of itself an interesting revelation, but the degree to which lymph-node enlargements may exist in the abdomen or thorax, or both, without giving rise to symptoms or signs of any sort until after the lapse of many months, is an astonishing illustration of the adaptability of the thoracic and abdominal viscera to gradually increasing pressure. Because of this fact it is impossible intelligently to estimate the duration of the disease. In the present series the average duration after the appearance of symptoms as related by the patients was twenty-five months—a figure which is probably of doubtful value, since historical data as related by the sick are notoriously unreliable. The shortest period was twenty days, the longest six years and two months. In 5 cases symptoms had been present for a period of three, seven (2 cases), eight and eleven

months. One case was of slightly more than a year's duration, 1 of two years' and 3 cases of over three years'. The longest case to be recorded, as far as I know, is by Cunningham, having a duration of twenty-five years.[20]

Treatment. No method of treatment thus far devised has been shown to influence the disease favorably for more than a short time, and even in such circumstances it may be difficult to judge the effects of treatment because of the proclivity of the enlarged lymph nodes to regress spontaneously or after intercurrent infections, or without apparent reason to remain stationary for an indefinite period. Surgical intervention is hopeless and should never be undertaken except for the mechanical relief of conditions which threaten life or are intolerable. Incidentally, the removal of tissue for diagnosis is a justifiable procedure, although it should be carried out with the precautions customarily observed in surgical operations. In the groin the operation, in my opinion, should be avoided since, in this region, infection is apt to occur and to be troublesome, sometimes fatal, as in one case in this series. Spread of the disease after removal of tissue for diagnosis, if it ever occurs, is to be regarded as a coincidence. In a somewhat comprehensive experience with Hodgkin's disease, clinically and otherwise, I have yet to encounter a regrettable incident following the removal of tissue for diagnosis, with the exception of the one just mentioned. The objection that this diagnostic procedure may be followed by rapid progression is gratuitous, and is based on the assumption that cells are liberated by operative manipulation and transplanted in remote parts, whereas it is known that Hodgkin's disease is not spread by the process of metastasis, but that it has multiple foci or origin, each of which is independent of the transplantation of cells through the blood or lymph streams from one lymph node to another or from the lymph nodes to other tissues.

In recent years it has been shown that the roentgen-ray treatment of Hodgkin's disease is often followed by remarkable diminution in the size of the diseased lymph nodes, but no instance of cure by this means has thus far been recorded. As far as I am aware, there is no acceptable explanation for the changes in the lymph nodes after roentgen-ray therapy. It has been claimed that the apparently beneficent effects of the roentgen-ray are due to vascular occlusion followed by the death of cells and replacement by connective tissue. In studying tissues in Hodgkin's disease that had been subjected to roentgen-ray treatment, I have seen the vascular and necrotic changes in question, but I have also seen them in tissues that had not been treated by this method. It remains to be decided whether the reparative alterations in question are to be accredited to man's therapeutic ingenuity or to some peculiar provision that Nature makes for tissues in distress.

Prognosis. The outlook in Hodgkin's disease is hopeless.

Summary and Conclusions. 1. Hodgkin's disease is divisible into two groups of cases: (*a*) Those in which the changes are confined to the lymphoid structures, *i.e.*, to the lymph nodes proper and to residual lymphoid foci in the spleen, in the walls of the portal vessels and in the interstitial tissues of the lungs, kidneys, bone-marrow, subcutaneous tissues, serous membranes, etc. In fact, it may display itself in practically any tissue of the body, since minute collections of lymphoid cells are of wide distribution and, in Hodgkin's disease, lymphoid tissue is a prerequisite to development. In the present series 10 cases, or 71 per cent, belong in this group. (*b*) The second group of cases is attended by changes of the same sort and in the same localities as in the group just mentioned, but in addition the disease brings about continuate infiltration and destruction of muscles, bloodvessels, serous and mucous membranes, erosion of bone and mechanical replacement of solid viscera. In this series 4, or 28 per cent, of the cases belong in this group.

2. It appears that we must relinquish the conception that Hodgkin's disease is most commonly shown by enlargement of the lymph nodes of the neck. In this series the disease displayed itself as an enlargement of the abdominal lymph nodes or of the abdominal and thoracic nodes in combination ten times more frequently. In the 14 cases of this series the lymph nodes of the neck were not enlarged at all in 4 (28 per cent). They were secondarily involved to a slight extent in 3 (21 per cent) and in 6 (43 per cent) they were more or less markedly enlarged, but always in association with collections in the deeper parts that were proportionately far more massive. In the remaining case (7 per cent) the cervical nodes were enormous. It is a fact of clinical value that enlargement of the axillary nodes is secondary to involvement of the thoracic or cervical nodes and that enlargement of the inguinal nodes is secondary to involvement of the abdominal nodes. These observations suggest that the provocative agent does not enter through the skin, but exclusively through mucous membranes, and probably only through the mucous membranes of the gastro-intestinal tract, although the respiratory tract cannot be excluded. It is significant, however, that in this series there was not a single case in which enlargement of the peribronchial nodes could be implicated other than as an associated phenomenon—never as the predominant focus. The brunt of attack in Hodgkin's disease is borne by the lymph nodes of the abdomen, thorax, neck, axilla and groin and by the auxiliary lymphoid system, including the spleen and liver and other residual lymphoid collections in various parts of the body; while that vast array of lymphoid follicles which lies in the submucosa of the gastro-intestinal, respiratory and urinary tracts practically always escapes intact. From this it is apparent that the provocative agent in Hodgkin's disease has a selective action on certain groups

of lymphoid tissue—a peculiarity which it shares with chronic lymphatic leukemia, in which disease the submucosal follicles are likewise apt to be spared.

3. Evidence is offered in this paper to show that Hodgkin's disease may reveal itself the most prominently in organs other than the lymph nodes—that enlargement of the spleen or the thymus or the liver may be the predominant feature, the associated lymph-node enlargements assuming a place of secondary importance.

According to our observations, Hodgkin's disease is divisible clinically and anatomically into five groups, as follows:

I. Hodgkin's disease of the regional lymph nodes:
   (*a*) Predominant involvement of the abdominal nodes (28 per cent).
   (*b*) Predominant involvement of the abdominal and thoracic nodes in combination (43 per cent).
   (*c*) Predominant involvement of the nodes of the neck (7 per cent).

II. Predominant involvement of the thymus.

III. Predominant involvement of the spleen.

IV. Predominant involvement of the liver.

V. (*a*) Axillary involvement (sequential to cervical or thoracic lymph-node enlargements).
   (*b*) Inguinal involvement (sequential to abdominal lymph-node enlargements).

4. In the present series the average weight of the spleen in 8 cases was 652 gm. in excess of the normal. In the ninth case the spleen was greatly enlarged, but its weight was not recorded. In the remaining 5 cases (35 per cent) the organ was normal in size or only slightly enlarged and could not be palpated during life. This latter finding is of practical application in view of the fact that palpable enlargement of the spleen is commonly regarded as a constant accompaniment of Hodgkin's disease.

In 7 cases the spleen was enlarged and nodular (50 per cent). In the remaining 7 cases no nodules were apparent in it and the shape of the organ was preserved. In this connection it is to be pointed out that the nodular condition of the spleen in Hodgkin's disease is of academic interest rather than of clinical value, since the nodules are distributed through the deeper substance of the organ and rarely, if ever, project to such an extent as to be palpable through the abdominal wall.

5. The present study emphasizes the fact that in Hodgkin's disease the skeletal muscles may be extensively destroyed by tissue of the same sort as that in the lymph nodes. In this series destructive changes are recorded in 3 cases, namely, in the intercostal and pectoral muscles in 1, in the pectorals and the psoas magnus in 1, and in the muscles of the forearm in 1.

6. The bone-marrow in Hodgkin's disease may react in at least

two different ways: (*a*) It may show hyperplastic changes, particularly in the eosinophiles and eosinophilic myelocytes; or (*b*) it may be replaced by tissue of identical composition with that of the diseased lymph nodes, sometimes over an extraordinarily wide distribution.

7. Evidence is presented in this paper which tends to show that in the reactions in the lymph nodes and in the bone-marrow there is a certain parallelism between Hodgkin's disease and chronic myelogenous leukemia. This suggests that the two diseases are fundamentally related and that they probably represent different quantitative responses to the *same type* of provocative agent.

8. Whether Hodgkin's disease is an inflammatory or a neoplasmic process remains to be determined. The fact that the histological composite tends to maintain its individuality throughout all changes of environment appears to me to constitute an argument in favor of its inflammatory nature.

9. Case VIII represents a new phase in the pathology of Hodgkin's disease, marked by massive enlargement of the liver, due to structural changes in the walls of the portal vessels that are strictly comparable to the changes encountered in the lymph nodes, including the characteristic cell composite and the overgrowth of connective tissue. Similar changes were present in the same case in the walls of the larger veins of the spleen and of the medulla of the suprarenal capsule. The abdominal lymph nodes were enlarged to a negligible extent, although in them the histological changes were characteristic.

10. Cases X and XI illustrate a rare finding in the pathology of Hodgkin's disease, namely, massive thickening of the pleura with focal areas of characteristic histology.

11. From the standpoint of symptomatology, Hodgkin's disease is a striking example of the adaptability of organs to gradually increasing pressure. Enlargement of the abdominal nodes or of the abdominal and thoracic nodes in combination or of the thymus may reach remarkable proportions before giving rise to symptoms of any description, or, at worst, to complaints from the patient that are trivial in proportion to the extent of the pathological changes in his body.

12. Hodgkin's disease is an affection of the hemolytopoietic apparatus. Its histogenesis is determined: (1) By preliminary hyperplasia of lymphoid cells in various parts of the body; and (2) by the discharge of mononuclear and multinuclear giant cells from the bone-marrow, with or without eosinophiles and eosinophilic myelocytes, and their arrest by the hyperplastic lymphoid depots in pursuit of their function as filters, the fibroblastic reaction in the recipient tissues representing a mechanical process designed to support the excess of cells by which they are burdened.

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NECROSIS AND GANGRENE OF THE URINARY BLADDER: REVIEW OF 153 CASES, INCLUDING 19 NOT PREVIOUSLY REPORTED.

By Charles C. Wolferth, M.D.,

and

T. Grier Miller, M.D.,

associates in medicine, university of pennsylvania, and assistant physicians, university hospital.

(From the Medical Division of the University Hospital and the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.)

Introduction. Necrosis and gangrene of the urinary bladder receive scant attention or are entirely ignored in clinical and pathological text-books. This is doubtless due to the fact that so few cases have been reported, Haultain,[1] in 1890, having found records of only 56, to which O'Neil,[2] in 1910, was able to add 52. These authors, as well as all others who have written on this subject, have excluded from consideration those bladder affections in which, although necrosis is recognized to have occurred at some stage of the pathological process, it has been overshadowed by some other outstanding lesion. Thus the necrosis that occurs in many vesical tumors, in various ulcerative lesions and in certain extensions of inflammation from without have not been dealt with; neither has that which develops in the course of formation of fistulous com-

munications of the bladder with other organs. We also have looked upon such necrotic processes as merely incidental, and have limited our investigations to a consideration of essentially necrotic or gangrenous lesions.

Excluding the new material presented in this paper, we have been able to collect 134 acceptable cases. This figure includes 2 cases of bladder gangrene in typhoid-fever patients (an apparently rare complication) which we[3] have recently reported. Since our recognition of those cases (within a year) another 1 of bladder gangrene and 2 of simple necrosis, none having any connection with typhoid fever, have been found on the medical service of this hospital and 2 others of gangrene have been studied by colleagues in another hospital, and by their permission are herein reported. In a search for more material we have examined in the laboratory of pathology of this university the records of 5250 autopsies, which were generously placed at our disposal by Prof. Allen J. Smith, and 14 additional cases have been found, 4 of which were diagnosed gangrene and 10, necrosis.

In view of this amount of previously unreported material (19 cases) which we have been able to assemble, it appears to us that necrosis and gangrene of the bladder are less rare than is indicated by the literature, and that the subject has not received the attention, either from clinicians or pathologists, that its importance warrants. Furthermore, many of the problems surrounding this highly interesting condition are still obscure. It has seemed worth while, therefore, to record the observations on our 3 recent cases and on 2 from the service of Dr. George Wilson at the Episcopal Hospital of Philadelphia, to present certain data on the material supplied by the pathological records of this medical school (see Appendix), to attempt a classification of all the available cases on the basis of the outstanding clinical conditions with which they have been associated and to discuss briefly various clinical and pathological aspects of the affection.

Nomenclature. The cases have been described under a great variety of names, including "gangrene of the bladder," "gangrenous cystitis," "exfoliation of the bladder," "exfoliative cystitis," "exfoliative necrosis of the bladder," "necrotic cystitis," "membranous cystitis" and a number of others. Some have been incorrectly designated "croupous," "diphtheritic" or "pseudomembranous cystitis."

The essential feature in all is death of bladder tissue *en masse*, or in other words, necrosis. Consequently, if all the cases are to be included under one name they should be called "necrosis of the bladder," as suggested by Haultain. In most instances, however, the dreadful fetor of the urine and the obvious putrefaction of the destroyed bladder tissue leave no doubt as to the presence of true gangrene. It may be that the gangrene is merely a secondary

change in necrotic bladder tissue, but to designate such a condition as "necrosis of the bladder" when gangrene is present is surely inadequate. For this reason we have preferred to retain in addition the name "gangrene of the bladder" for those cases to which it is clearly applicable—not in any attempt radically to differentiate gangrene from simple necrosis, but in order to draw attention to the characteristic and striking clinical features of the former group of cases.

"Exfoliative cystitis" and "exfoliation of the bladder" should be dropped from the nomenclature. Exfoliation of the dead tissue may be expected always to occur if the patient recovers or the illness is sufficiently protracted, but it is merely an incidental, although sometimes a spectacular, occurrence in the course of the disease. Such designations, moreover, give no scientific idea as to the nature of the lesion.

Review of the Literature. Attention was first attracted to necrotic or gangrenous lesions of the bladder by the passage of exfoliated tissue *per urethram*. Large fragments or even complete casts of the bladder not infrequently have been extruded. According to Haultain,[1] the earliest writers to mention exfoliation of the bladder were Willius (1650), Ruysch and Morgagni. Tulpius,[4] in 1715, reported a case in which a membrane was passed with crystals adherent to it. These early writers all believed the exfoliated material to be bladder tissue, but Fontaine[5] (1815) and Andral[6] (1829) contended that it was false membrane. Finally, in a case of Lever's[7] (1852) the exfoliated membrane was examined microscopically by Gull, who demonstrated that bladder tissue was present. This finding has since been confirmed in many other cases. It has likewise been shown that false membrane containing no bladder tissue may be exfoliated and passed *per urethram*, and such exfoliated material usually has been called "pseudomembranous," "diphtheritic" or "croupous." Guyon[8] eventually clearly differentiated these two conditions as separate entities, and his opinion has been generally accepted. Aschoff,[9] however, states that there is a variable amount of necrosis of the bladder wall even in diphtheritic cystitis. The relationships of these conditions will be discussed later.

Much has been written regarding the etiology of the condition, and this also will be referred to under the appropriate heading, but it is proper to say here that neither clinical observations nor experimental methods have as yet led to any unanimity of opinion or to any well-established facts regarding this phase of the subject. This is perhaps partly due to the fact that the available information regarding its pathological-histology is limited largely to that obtained from examinations of exfoliated materials and to a few brief descriptions of the microscopical appearance of the bladder walls. It is also in part due to the scarcity of data on the bacteri-

ology of the condition, especially in its early stages. On the other hand, the clinical course of the disease, the symptoms and the character of the urine have been fully and carefully described in many cases, even by the earlier writers, so that there is a great deal of data and more or less uniformity of opinion on these subjects.

On the whole it may be said that very little progress has been made in our knowledge of necrosis or gangrene of the bladder since Haultain's[1] review of the subject in 1890.

Report of Cases (Five in Number). CASE I.—*Gangrene of Bladder.* M. K., white, female, aged fifty-five years, was admitted to the medical division of the University Hospital on September 28, 1922, on account of pain in the lower abdomen and inability to void urine. She was semistuporous, answering simple questions with difficulty, so that it was necessary to obtain the history from her husband. He stated that she had fallen and injured her head four or five years previously, and had not been mentally clear since. For three or four years she had had frequency of urination and occasional retention, but the trouble had always passed off without medical treatment. The attack which brought her to the hospital began three weeks before her admission and was characterized by pain in the lower abdomen, becoming more and more severe, and some abdominal enlargement.

On admission the temperature was 99.8° F., the pulse-rate 120 and the respiratory frequency 28. The pulse was of very poor quality and the blood-pressure 95/75. The left pupil was larger than the right, but both were regular and reacted to light. The lips were dry and sordes were present. The tongue was dry and beefy in appearance. Examination of the thorax was negative. The lower abdomen was greatly enlarged, tense and tender on pressure.

She was immediately catheterized by a nurse but only a small amount of urine was obtained. Shortly afterward the resident physician was more successful, obtaining 2100 cc of bloody, alkaline urine, and at the end a large amount of thick pus. The passage of the catheter was easy but very painful, apparently on account of inflammation and excoriation about the urethra. A pelvic examination showed the uterus to be small and in anteposition. There were no adnexal masses palpated.

During the next few days catheterization and irrigation of the bladder were performed frequently, and, although the urine remained bloody and contained a large amount of pus, there appeared to be some clinical improvement. The pulse became stronger, the blood-pressure rose to 110/60 and she was less dull mentally. The temperature varied between 97 and 99.6° F. and the pulse between 85 and 120. On October 4 she voided 300 cc of urine voluntarily and one specimen was reported acid in reaction.

On October 5 a cystoscopical examination by Dr. Floyd E. Keene was reported upon as follows: "Bladder capacity, 240 cc. The whole dome of the bladder presents a shaggy gangrenous mucosa. The bladder base presents large areas of fibrino-purulent deposit with here and there areas of intense redness which represent either a cystitis or areas of exfoliated mucosa. Because of the diffuse coating of the bladder base, it is impossible to define accurately the underlying lesion, but examination *per* vagina discloses intense induration of the bladder base, and the underlying lesion is, in all probability, malignant."

The urinary output was good, never falling below 1100 cc per day. The highest specific gravity was 1022. All but one specimen were alkaline, all were reddish to dark red in color, due to the presence of blood, and pus was abundant. The urine was fetid for several days after admission, then the odor became merely ammoniacal until two days before death, when it again became fetid. Numerous small grayish-white fragments were passed through the catheter, none of those observed being more than 1 or 1.5 cm. in length. Many of these fragments were examined for bladder tissue, but all were negative. They consisted principally of pus cells with a slight admixture of erythrocytes.

Microörganisms were abundant in the urine constantly. Aërobic cultures showed principally hemolytic streptococci and a member of the proteus group. Anaërobic cultures were negative for Bacillus neigeux and other anaërobic organisms of this type.

On admission the leukocyte count was 20,200 with 83 per cent of polymorphonuclear cells. There were 4,100,000 erythrocytes and 74 per cent of hemoglobin. The leukocyte count rose steadily and the last one, made on October 6, was 41,200. The blood and spinal-fluid Wassermann reactions were negative. The cell count and the colloidal-gold curve of the spinal fluid were also negative. The blood-urea nitrogen on September 30 was 50 mg. per 100 cc and on October 6, 30 mg.

Death occurred October 9, and although no autopsy was permitted a digital exploration of the bladder was made. The wall appeared to be uniformly thickened, and there were no localized areas of induration or masses of any kind. It was friable and easily ruptured by the finger. Several fragments were withdrawn for microscopical examination. These showed the wall to be nearly 1 cm. in thickness. The tissue was foul-smelling and the inner surface gangrenous in appearance. There was no evidence of inflammation on the exterior surface.

A microscopical section showed that there was present some normal epithelium, the continuity of which was broken in places and in its stead there was an irregular mass of tissue consisting of debris, small round cells, polymorphonuclear cells and blood. This necrosis did not extend very deeply into the submucosa.

The submucous layer was greatly thickened, showing an overgrowth of young fibrous connective tissue with a moderate degree of infiltration of small round cells and congestion of the blood-vessels in certain areas. In one or two places there was marked infiltration of small round cells and there were also some scattered giant cells with three to four nuclei in each. The muscular layers were intact and of normal thickness. The cells and fibers stained clearly and showed no degeneration. Between the fibers there was a slight increase in small round cells. The interfibrous coat was of average thickness and showed no abnormal changes.

Comment. Both the history of this patient and the histo-pathology of the bladder point to a cystitis much older than the acute condition which brought her to the hospital. The etiology of this chronic cystitis could not be determined. The development of gangrene was undoubtedly contributed to by the occurrence of extreme urinary retention in a bladder that was almost certainly already the seat of infection. No evidence could be obtained to support the recent contention of Legueu that Bacillus neigeux is responsible for gangrene of the bladder, although several special cultures were made in an effort to recover this or other anaërobic organisms.

CASE II.—W. P. C., white, male, a fireman, aged sixty-seven years, was admitted to the service of Dr. George Wilson at the Episcopal Hospital of Philadelphia (reported through the courtesy of Dr. Wilson and Dr. C. Y. White, the pathologist) on January 15, 1923, because of weakness and difficulty in passing his urine. He had been confined to bed for four days before admission. In August, 1922, he had suffered from an apoplectic attack which affected his left leg only.

Physical examination revealed good general development and nutrition, some emphysema, left-sided cardiac enlargement with a systolic murmur and urinary bladder distention, which necessitated catheterization. He soon developed a numbness in his right leg with disability and incontinence of feces.

A *neurological examination* on January 20 by Dr. Wilson showed a complete paraplegia, with typical positive bilateral Babinski reflexes and absent deep tendon reflexes. On January 27 bloody alkaline urine was obtained *per* catheter, and some shreds were observed. There was considerable pain and distress in the bladder area. At this time a cystoscopical examination revealed what was considered a sloughing malignant lesion of the bladder wall. It was believed that there had occurred from this metastasis to the vertebræ.

The patient died on February 4, and necropsy showed a carcinoma of the prostate and of the vertebræ, but only ulceration and gangrene of the bladder wall itself, with coils of intestine adherent

to the fundus of the bladder. The contents of the bladder were greenish, purulent and of foul odor. The mucous membrane was entirely destroyed and the wall was friable throughout.

The *microscopical sections* were reported upon as follows: Prostate shows malignant adenoma, papillary in places. The bladder wall may be described as the seat of two distinct processes. The muscular layer shows fibrosis and chronic progressive inflammation with involvement of the muscle bundles, some of which are changed into fibrous bands, others show granular degeneration and vacuolization, while some of the muscle groups are normal. Internal to the muscular layer is a thin zone of granulation tissue upon which lies a polymorphonuclear zone, internal to which the tissue is completely necrotic. Arterioles and capillaries remain patent up to the zone of granulation tissue. Some small thrombotic veins, however, can be found in this area. In none of the sections is there evidence of extension from the tumor in the prostate.

Diagnosis. Chronic fibrous inflammation of the outer layers of the bladder wall; acute, purulent and necrotizing processes internal to this.

Comment. This case also illustrates the difficulty of differentiating gangrene from carcinoma of the bladder, even when cystoscopical study is made. Three possible factors exist for the production of the gangrene: Urinary retention, a central nervous system lesion and infection.

Case III.—A. C., female, white, aged forty-seven years, was admitted to the service of Dr. George Wilson at the Episcopal Hospital (reported through the courtesy of Dr. Wilson and Dr. C. Y. White) on December 6, 1922, on account of pain in the back and inability to move her legs. In the preceding September she had struck her leg against a table, and two days later an inflammatory lesion requiring incision was recognized. At about this time there had developed a knife-like pain around her waist. Three days before her admission she became unable to move her legs, this paralysis having come on gradually and with much pain. For these three days also she had been unable to void urine voluntarily and had been catheterized. There was no incontinence of urine. On admission she complained mainly of some numbness in the legs.

Examination revealed an obese woman, with a flaccid paraplegia and some general pallor of the skin and mucous membranes. The right pupil was larger than the left and irregular and the tonsils were diseased. The plantar and patellar reflexes were absent. The abdominal reflexes were lost. There was some disturbance of the pain and temperature sense in the right lower extremity. The sense of position was intact in both great toes. There was generalized abdominal tenderness with angulation at about the

sixth dorsal vertebra, and a roentgen-ray showed absorption of the bodies of the fifth and sixth thoracic vertebræ. The urine showed a low specific gravity, a trace of albumin and occasional light and dark granular casts, but only a few leukocytes, though no examinations were recorded after December 7. She died on December 15.

Autopsy revealed a neoplasm of the vertebræ and gangrenous cystitis. The bladder wall was thickened, the mucous membrane gangrenous and the urine purulent.

Microscopical sections of the bladder wall were reported upon as follows: The inner layer is fibrinous with an infiltrate of polymorphonuclear cells. It is necrotic, but there is no massive slough present in the sections examined. Cellular infiltrate and some fibrin may be seen between the muscle bundles, some of which have been partly destroyed. About the middle of the bladder wall bloodvessels are quite numerous, in some places having well-developed walls associated with considerable amount of connective tissue. This suggests that chronic inflammation had existed prior to the recent necrotizing processes. Small hemorrhages may also be found in the muscular layer. Beneath the fibrous layer there is also a recent fibrino-cellular change. The process seems like a severe acute necrotizing one, fairly well distributed through all layers of the bladder wall.

Comment. There was nothing elicited in the clinical study to account for the histological evidences of chronic inflammation of the bladder. Cystitis may have occurred during the period of illness prior to paralysis and acute retention. The chronic inflammation of the bladder presented a favorable soil for the development of an acute necrotizing process following retention and catheterization. Thus, as in Case II, there are three possible factors in the production of the bladder lesions: Retention, infection and central nervous system disease.

Case IV.—*Necrosis of Bladder.* Mrs. E. K., white, married, aged seventy-two years, was admitted to the medical division of the University Hospital, May 28, 1922, and died two days later. The patient was so ill that no history could be obtained beyond the fact that she had been short of breath for about a year and had been told by her physician that she had diabetes. The physical examination showed signs of extreme cardiac failure. There were marked dyspnea, cyanosis and edema, a large effusion in the right chest and a greatly enlarged liver. The heart area was greatly increased and auricular fibrillation was present. There was advanced arteriosclerosis of the radial, brachial and retinal vessels. The blood count was normal and the blood Wassermann test negative. The blood sugar was 0.273 per cent.

Only one urine specimen was obtained. It was amber, contained a flocculent sediment, had a specific gravity of 1.029, was acid and

showed a cloud of albumin and some sugar, but was negative for acetone.

Microscopically, it revealed a few narrow hyaline, light granular and epithelial casts, no mucus, no erythrocytes, 85 to 100 leukocytes per high-power field, a few epithelial cells and no crystals.

The right chest was tapped and 400 cc of fluid removed, but this did not bring about any improvement. Death appeared to be due to heart failure.

Autopsy showed advanced aortic sclerosis with ulceration; cardiac hypertrophy; coronary arteriosclerosis; beginning cardiac aneurysm; terminal congestion and edema of the lungs; lobular pneumonia in the right lower lobe; sclerotic changes in the spleen, kidneys, pancreas and liver.

The urinary bladder was normal in size. The inner aspect of the wall was here and there definitely reddened and in a few places there were necrotic areas, greenish-red in color and averaging several millimeters in diameter. The rest of the inner wall, however, was gray, entirely unbroken and almost normal in appearance.

On microscopical examination, the mucosa was found completely destroyed in two sections of the necrotic areas examined, and replaced by a fibrino-cellular exudate. The fibrin occurred in the form of broad strands, rather than as a fine network. The submucosa and even part of the muscularis were likewise destroyed and replaced by similar foreign material. The portion of muscularis which was left presented a moderate separation of the poorly staining swollen muscle fibers. The serosa was normal.

Comment. The only antemortem finding that could be regarded as pointing toward an affection of the bladder in this case was the excess of leukocytes in the urine, but on account of the desperate condition of the patient symptoms may have been masked. There was, however, no retention. The necrosis obviously was in a very early stage and what its eventual outcome might have been, had the patient lived longer, may only be conjectured. The condition was of pathological, rather than clinical interest.

CASE V.—Mrs. S. L., white, a widow, aged forty-three years, was admitted to the medical division of the University Hospital, August 25, 1922, in an advanced stage of cardio-vascular-renal disease. There was tremendous cardiac enlargement, passive congestion of viscera and edema of dependent parts of the body. A hard nodular mass palpated in the right hypochondrium, was thought to be a diseased gall-bladder. The systolic blood-pressure was consistently above 200 and the diastolic varied between 120 and 140. Examinations of the urine and the results of kidney function tests indicated advanced renal insufficiency. The patient showed no response to treatment and the evidences of cardiac failure and renal insuffi-

ciency increased. During the last few weeks of life large abscesses developed in various parts of the body. Urine examinations were made routinely and showed no excess of leukocytes until three days before death (which occurred on November 10), when they were reported as numerous. The final specimen was acid in reaction and no red cells were found. No symptoms referable to the bladder were noted, but this may have been due to the fact that the patient was irrational for several days before death.

Autopsy performed four hours after death showed widespread arteriosclerosis, marked cardiac hypertrophy and coronary sclerosis, chronic glomerular and tubular nephritis, gall stones and empyema of the gall-bladder. The urinary bladder was normal in size. The mucosa was exceedingly reddened and the submucous vessels greatly congested. Near the urethral opening there were several superficial frankly necrotic areas varying from 5 mm. to 2 cm. in diameter. The lesions were pale, dirty gray and rough in appearance and the edges were slightly raised.

Comment. This case in its clinical and pathological aspect resembles Case IV.

Etiology. Various causes have been assigned for the development of necrosis and gangrene of the bladder wall, but no particular one of them seems satisfactory for all the cases. Cossy[10] (1843), analyzing various possible factors for the production of this complication in his series of typhoid-fever patients, concluded that the gangrene which he described was due to some unknown but inherent characteristic of the particular epidemic which he encountered. Haultain[1] (1890) believed that deficient nutrition was the basal factor, this resulting from mere urinary retention in some cases (interfering with the venous circulation) and in others from outside pressure on the neck of the bladder (labor and impacted pelvic masses). O'Neil[2] (1910) adhered to Haultain's theory, but in addition called attention to a group that could be explained only by infection, while Mock[11] (1911) and others (see Table VII) report cases in which chemical irritants were obviously of etiological significance. Cathelin[2] (1919) emphasized the primary importance of some central nervous system lesion and looked upon retention, catheterization, irritants, etc., as only secondary factors. Pepin,[13] Legueu[14] and Economos[15] have championed the infectious theory; Legueu insisting that only certain anaërobic organism were causative.

Experimental necrosis of the bladder has been produced by May[16] and by Heubner.[17] The former showed that continuous artificial urinary retention in dogs until death (sixty hours in two experiments) produced extensive hemorrhage in the bladder wall and separation of the mucosa and submucosa at the fundus by extravasation. When retention was produced intermittently the mucosa and submucosa were broken down and filled with granular

material. Heubner ligated the neck of the bladder in rabbits, thus obstructing the arterial supply, for periods as short as two hours and then allowed the circulation to resume. The animals were killed at various intervals thereafter, from within a few hours to five or six days, and necrosis of the bladder was found. He concluded that even temporary disturbance of bladder circulation could bring about necrosis. These experiments of May and of Heubner have been cited frequently in support of the view that mechanical disturbance rather than infection is the important etiological factor.

In an attempt to make use of our collected data for the elucidation of this problem we have assembled the cases, insofar as possible, in accordance with the presence and apparent importance of certain outstanding clinical features. For instance, in Table I are grouped all the cases reported in women who were pregnant and who had retrodisplaced uteri. It will be seen that all of these had retention, due in the main to outside pressure, and that many of them had been catheterized. It is probable that in all of them, though it is not so stated in the reports, catheterization had been performed, thus affording in addition an opportunity for infection. Among the 21 labor cases (Table II) only 15 are reported as having had retention, but pressure on the neck of the bladder was a possible factor in all. It was these cases together with those under Table III (pelvic masses), in 3 of which it is stated that retention did not occur, that originally led Haultain to the belief that gangrene might develop not only from retention but also as a result of pressure on the neck of the bladder, shutting off the arterial circulation.

In Table IV (cystitis) there is clear evidence of a bladder infection. In Table V (stricture of urethra) 6 of the 7 cases had retention and possibly the seventh did also, though it is not so stated. It may be safely assumed, furthermore, that all these were catheterized, and as well those of Table VI (stone in bladder). The etiological significance in Table VII of the irritants injected cannot be doubted. Of those cases occurring in patients with typhoid fever, pneumonia and acute malignant endocarditis (Table VIII) 6 are reported to have had urinary retention, while 2 did not. In this table blood infection would seem to have been a possibility. Central nervous system lesions (Table IX), as is well known, do frequently give rise to trophic disturbances, but they also often give rise to urinary retention; and in view of the small number of such bladder disturbances in comparison with the large number of central nervous system lesions, even with retention, it is perhaps fair to assume that the trophic influence is not the primary cause. This is especially true since it cannot be invoked to explain the many other necrotic and gangrenous bladder cases. Trauma (Table X) may readily give rise to retention and subsequent catheterization with infection, or it may involve actual penetration of

the tissues (even the bladder itself) from the outside, thus more directly bringing about an infective condition. Various of these factors may have been operative in our miscellaneous group (Table XI).

TABLE I.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN PREGNANT WOMEN WITH RETRODISPLACEMENT OF THE UTERUS.

Author	Reference.	Age.	Urinary retention.	Catheterized.	Character of urine.*	Exfoliation.	Depth of the lesion.†	Result.‡
1. Van Doeberen	Observat. Acad. Gronigæ, 1765, p. 83	20	+	0	B	+	Per.	D
2. Lynne	Med. Observat. and Enquir., 1771, **5**, 388	40	+	+	..	+	..	D
3. Naumberg	Stark's Arch., 1796, **6**, 381	34	+	0	B	+	..	D
4. Saxtorph	Gesammelte Abhandlungen, 1803, **1**, 261	..	+	..	..	+	..	D
5. Zeitfuchs	Seibolds Jahrb f. Geburtsh., 1833–1834, **13**, 99	38	+	+	BPA	+	1	L
6. Kiwisch Ritter von Rotterau	Vrtljschr. f. Heilkunde, 1844, **2**, 37	28	+	+	BP	+	1	L
7. Wittich	Neue Ztschr. f. Geburtsh., 1847, **23**, 98	28	+	..	BP	+	3	L
8. Luschka	Virchow's Arch. f. path. Anat., 1854, **7**, 30	26	+	+	..	+	2	D
9. Rosenplanter	Quoted from Haultain, Inaugural Dissertation, Dorpat, 1856	..	+	..	..	+	2	L
10. Bamberger	Thésis, Paris, 1860, p. 64	..	+	..	..	..	..	D
11. Dray	Quoted from Haultain, Med. and Phys. Jour., 1860, p. 456	..	+	..	..	..	..	D
12. May	Inaugural Dissertation, Giessen, 1862	..	+	..	..	+	2	D
13. Haussmann	Monatsschr. f. Geburtsh., 1868, **31**, 132	39	+	+	FA	+	1	L
14. Schatz	Arch. f. Gynäk., 1870, **1**, 469	35	+	..	PF	+	3	D
15. Southey	Lancet, 1871, **1**, 610	16	+	+	FA	+	4	D
16. Godson	Brit. Med. Jour., 1871, **2**, 432	26	+	+	BFA	+	4	L
17. Wardell	Brit. Med. Jour., 1871, **1**, 613	28	+	..	F	+	1	L
18. Gervis	Obst. Trans., 1874, **16**, 233	33	+	+	BF	..	..	D
19. Gervis	Obst. Trans., 1874, **16**, 233	36	+	+	B	..	..	D
20. Moldenhauer	Arch. f. Gynäk., 1874, **6**, 108	33	+	..	BFA	+	3	D
21. Williams	Obst. Trans., 1874, p. 258	..	+	..	..	+	1	D
22. Brandeis	Arch. f. Gynäk., 1875, **7**, 189	36	+	..	BFA	+	1	L
23. Frankenhauser	Arch. f. Gynäk., 1877	39	+	+	BPF	+	4	L
24. Madurowicz	Wien. med. Wchnschr., 1877, p. 2167	27	+	..	BPFA	+	4	L
25. Veit	Samml. klin. Vortr., Leipsig, 1879	..	+	..	..	+	1	D
26. Veit	Samml. klin. Vortr., Leipsig, 1879	40	+	..	BPF	+	1	L
27. Kleim	Inaugural Dissertation, Berlin, 1880	33	+	..	BPFA	+	3	D
28. Moreau	Quoted from Haultain.	..	+	..	..	..	Per. 4	D
29. Krukenberg	Arch. f. Gynäk., 1882, **19**, 261	33	+	..	PFA	+	4	D
30. Walters	Obst. Trans., London, 1883, **25**, 33	..	+	..	..	+	1	L
31. Valenta	Memorabilien, 1883, **28**, 1	..	+	+	F	+	Per. 4	D
32. Hurry	Edinburgh Jour., 1884, **29**, 1000	34	+	..	BPA	+	2	D
33. Pinard	Ann. de gynéc. et d'obst., 1886, **26**, 338	21	+	..	BPFA	+	3	D
34. Corkhill	Lancet, 1887, **2**, 1311	28	+	..	BPFA	+	..	L
35. Hartmann	Bull. Soc. anat. de Paris, 1888, **63**, 518	21	+	..	BPFA	+	3	D
36. Rasch	Tr. Obst. Soc., London, 1889, **31**, 129	..	+	..	B	..	..	D
37. Haultain	Rep. Lab. Roy. Coll. Phys., Edinburgh, 1890, **11**, 185	26	+	..	BF	+	4	D
38. Haultain	Rep. Lab. Roy. Coll. Phys., Edinburgh, 1890, **11**, 185	43	+	..	BF	..	2	D
39. Oliver	Lancet, 1890, **1**, 638	..	+	..	F	..	4	D
40. Cockram	Med. News, 1893, **63**, 633	30	+	..	BF	+	1	L

Footnotes (applicable to all the tables).

* "B" indicates bloody; "P," purulent; "F," fetid; "A," alkaline.

† "1" represents involvement of the mucosa only; "2," of the mucosa and submucosa; "3," of mucosa, submucosa and muscular layer; "4," of the entire bladder wall; "Per" represents perforation of bladder wall.

‡ "D" represents death and "L" recovery.

TABLE II.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER DEVELOPING IN WOMEN AFTER LABOR.

Author.	Reference.	Age.	Retention.	Catheterized.	Character of urine.	Exfoliation.	Depth of the lesion.	Result.
1. Hunter	Med. Observ. and Enquir., 1771, **4**, 58	38	+	+	B	+	..	D
2. Barnes	Med. Times, 1861, **1**, 186	..	+	+	BF	+	1	L
3. Hewitt	Quoted from Haultain, Med. Times and Gaz., 1863, **11**, 522	..	..	..	..	+	..	L
4. Martyn	Path. Trans., London, 1863, **15**, 137	40	+	+	PFA	+	3	L
5. Wells	Med. Times and Gaz., 1863, **15**, 140	22	+	..	BA	+	3	D
6. Wells	Med. Times and Gaz., 1863, **15**, 140	..	?	+	BPA	+	4	L
7. Whitehead	Brit. Med. Jour., 1871, **2**, 432	..	+	+	..	+	1	L
8. Phillips	Brit. Med. Jour., 1871, **1**, 662	21	+	..	..	+	2	L
9. Bell	Edinburgh Med. Jour., 1875, **20**, 935	..	..	..	..	+	1	L
10. Maurer	Inaug. Dissertation, Berlin, 1880	31	+	+	BPFA	+	2	L
11. Doran	Obst. Trans., London, 1881, **23**, 2	31	+	+	BA	+	3	L
12. Ribnikar	Inaug. Dissertation, Zurich, 1882	36	+	..	..	..	1	D
13. Otis	Boston Med. and Surg. Jour., 1883, **31**, 458	26	+	+	BFA	+	2	L
14. Aveling	Obst. Trans., London, 1883, **25**, 33	..	+	+	BF	+	1	L
15. Boldt	Am. Jour. Obst., 1888, **21**, 350	18	?	+	BPFA	+	3	D
16. Favell	Lancet, 1900, **2**, 1352	..	..	..	..	+	1	D
17. Stoeckel	Monatsschr. f. Urol., 1902, **7**, 201	..	..	0	BPF	+	2	L
18. Arroyo	Quoted from O'Neil	25	+	+	F	+	2	L
19. O'Neil	Surg., Gynec. and Obst., 1910, **10**, 503	33	+	+	B	+	..	L
20. O'Neil	Surg., Gynec. and Obst., loc. cit.	30	+	+	FPB	+	..	L
21. Adrian	Deutsch. med. Wchnschr., 1910, **36**, 1585	32	+	+	BP	+	3	L

TABLE III.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN WOMEN WHO SUFFERED FROM EXTERNAL PRESSURE ON THE URINARY APPARATUS, EXCLUSIVE OF THOSE REFERRED TO IN TABLES I AND II.

Author.	Reference.	Age.	Retention.	Catheterized.	Condition giving rise to pressure.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Litzmann	Arch. f. Gynäk., 1880, **16**, 323	35	+	+	Extrauterine pregnancy	B	..	4	D	Perforation of bladder.
2. Lohlein	Ztschr. f. Gebrtsh. u. Gynäk., 1888, **14**, 534	36	+	+	Uterine fibroid; operated	BPFA	..	2	D	Operation possible cause.
3. Haas	München. med. Wchnschr., 1889, **36**, 401	..	0	0	Vaginal tampon	BP	+	2	L	Tampon inserted after abortion.
4. Southam	Med. Chron., Manchester, 1892, **17**, 230	42	0	..	Pessary	BPFA	+	3	L	Cystitis preceded gangrene.
5. Gottberg	Inaug. Dissertation, Marburg, 1892	18	+	+	Hematometra	A	+	2	L	Operated on.
6. Gottberg	Inaug. Dissertation, Marburg, 1892	42	+	+	Myoma uteri	BF	+	..	L	Trauma; was thrown from sleigh.
7. Vahle	Inaug. Dissertation, Marburg, 1899	48	+	+	Incarcerated myoma uteri	P	..	3	D	
8. Plaut	Inaug. Dissertation, Marburg, 1899	..	..	..	Extrauterine pregnancy	..	..	..	D	Peritonitis, sepsis.
9. Stoeckel	Monatsschr. f. Urol., 1902, **7**, 201	32	..	..	Vaginal tampon for the bleeding	BPF bac.	+	2	L	Late pregnancy; vesico-vaginal fistula developed.
10. Barlet	Brit. Med. Jour., 1912, **1**, 122	26	0	0	Vaginal tampon	BP acid	+	3	L	Late pregnancy.
11. Wernitz	Gynäk. Rundschau., 1912, **6**, 208	19	+	+	Hematocolpos	BPFA	+	3	L	

TABLE IV.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN WHICH CYSTITIS WAS THE ONLY DISCOVERABLE CONDITION OF PROBABLE ETIOLOGICAL SIGNIFICANCE.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Lever . .	Guy's Hosp. Rep., 1853, **8**, 49	F	28	+	..	PF	+	3	L	"Nervous shock."
2. Buchanan .	Brit. Med. Jour., 1871, **2**, 520	M	60	+	+	...	+	1	L	
3. Kermisson .	Bull. Soc. anat. de Par., 1875, 10, 291	M	55	..	..	PA	+	2	D	
4. Dubard .	Bull. Soc. anat. de Par., 1877, **52**, 281	F	65	..	..	BF	+	3	D	
5. Jacobi . .	New York Med. Jour., 1882, **36**, 304	M	66	+	+	BPF	+	1	D	
6. Lockhart .	Montreal Med. Jour., 1891, **20**, 1	F	28	+	+	PA	+	3		
7. Warren .	Boston Med. and Surg. Jour., 1896, **134**, 641	F	38	..	..	BPA	+	2	L	Surgical dilatation of the vagina.
8. Norris . .	Am. Med., 1906, **11**, 478	F	32	..	+	BP	+	3	L	
9. Esau . .	Folia Urol., 1907–1918, **1**, 582	M	63	+	+	BPFA bac.	+	..	L	Postoperative cystitis.
10. Prigl . .	Ztschr. f. Urol., 1909, **3**, 163	F	43	0	..	BPFA bac.	+	3	L	Old tuberculosis of kidney and bladder.
11. Warren Museum*	Quoted from O'Neil	M	35	..	..	BPF	+	1	D	Suprapubic operation.
12. Legueu . .	Jour d'urol., 1917–1918, **7**, 105	M	21	+	+	BPF bac.	+	3	L	Postoperative pyelonephritis.
13. Wolferth and Miller	Appendix, this report 4425 (No. 13)	M	48	..	..	BF	..	3	D	Enlarged prostate.
14. Wolferth and Miller	This report, Case I	F	55	+	+	BPFA	+	2	D	

* Specimen No. 4968, Harvard Medical School.

TABLE V.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER OCCURRING IN MEN WITH STRICTURES OF THE URETHRA.

Author.	Reference.	Age.	Retention.	Catheterized.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Bose . . .	Bull. Soc. anat. de Par., 1827, **2**, 84	72	+	+	FA	+	1	D	
2. Hall . . .	Proc. Phila. Path. Soc., 1860, **1**, 6	36	+	..	FBA	..	..	D	Catheterization attempted, but failed.
3. Schrady . .	New York Med. Record, 1884, **25**, 79	45	+	..	FA	+	..	L	Perineal section performed.
4. Tronchet .	Quoted from O'Neill.	75	+	..	FA	+	2	D	Diabetes.
5. St. George Hospital* .	Quoted from Pepin	..	..	..	..	+	2	D	
6. Lennander and Lundberg	Quoted from Pepin, Upsala Läkaref. Förh., 1897, **3**, 563	53	+	..	BPA bac.	+	3	D	Also enlarged prostate.
7. Nogues (Economos)	Jour. d'urol., 1922, **13**, 37	54	+	..	BPF bac.	+	3	D	Kidney abscesses.

* Specimen, Series 39, Subseries 8.

TABLE VI.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER OCCURRING IN PATIENTS WHO HAD A STONE IN THE BLADDER.

Author.	Reference.	Sex.	Age.	Retention.	Catheterised.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Dolbeau . .	Traité Pratique de la Pierre dans la Vessie, 1764, p. 314 (quoted from Pepin)	M	26	+	+	PA	+	3	L	Cystotomy.
2. Dolbeau . .	Traité Pratique de la Pierre dans la Vessie, 1764, p. 314 (quoted from Pepin)	M	14	..	..	..	+	2	L	Cystotomy.
3. Deschamps .	Traité de la Taille, 1796 (quoted from Pepin)	M	..	..	..	FP	+	..	L	Cystotomy.
4. Stein . .	Jour. Cutan. and Genito-urin. Dis., 1894, **12**, 273	M	26	+	+	BPFA	+	2	D	Cystotomy.
5. Dean . .	Practitioner, 1904, **72**, 907	M	18	+	+	P	+	..	L	Stone in urethra; cystotomy.
6. Praeger . .	München. med. Wchnschr., 1906, **53**, 1275	F	38	+	..	BPF	+	1	..	Pregnancy; abortion.

TABLE VII.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER DEVELOPING AFTER THE INJECTION INTO THE BLADDER OF IRRITANTS.

Author.	Reference.	Sex.	Age.	Retention.	Catheterised.	Substance injected.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Begouin .	Arch. clin. de Bordeaux, 1892, **1**, 479	F	20	0	..	Sodium chloride	B	+	3	L	
2. Robinson	Albany Med. Ann., 1907, **28**, 175	F	40	..	..	Hot normal salt solution, boric acid and vinegar	..	+	1	L	Necrosis due to irrigation or cystitis?
3. Mock .	Ann. d. mal. de'org. génito-urin., Paris, 1911, **2**, 1633	F	25	+	+	Ammonia solution	BPFA	+	3	L	Also pyelitis.
4. Mock .	Ann. d. mal. de'org. génito-urin., Paris, 1911, **2**, 1633	F	19	..	..	Sodium chloride and vinegar	..	+	3	L	Residual cystitis and pyelonephritis.
5. Morson .	Brit. Med. Jour., 1919, **1**, 129	M	27	0	..	Potassium permanganate	B	..	3	D	Also gangrene of lungs.
6. Dawson .	Bull. Johns Hopkins Hosp., 1919, **9**, 155	M	23	0	..	Potassium permanganate	No P No B	+	1	L	Only epithelium exfoliated.

TABLE VIII.—CASES OF NECROSIS OR GANGRENE OF THE BLADDER OCCURRING IN THE COURSE OF GENERAL INFECTIONS.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Infection.	Character of urine.	Exfoliation.	Depth of lesion.	Results.	Remarks.
1. Cossy . .	Arch. gén. de méd., 1843, **3**, 24	F	18	0	..	Typhoid	..	..	..	D	Gangrene in patches.
2. Cossy . .	Arch. gén. de méd., 1843, **3**, 24	F	..	+	+	Typhoid	BFA	+	1	D	
3. Cossy . .	Arch. gén. de méd., 1843, **3**, 24	F	21	+	+	Typhoid	F	..	..	D	
4. Lemaire .	Bull. Soc. anat. de Paris, 1863, **38**, 416	F	..	+	+	Typhoid	F	+	2	D	
5. Perriol . .	Le Dauphine méd., 1912, **36**, 49	F	25	+	..	Typhoid	BPF	+	3	L	
6. MacGowan	California State Jour. Med., 1918, **16**, 21	F	..	..	..	Pneumonia	BPFA	+	..	L	
7. Miller and Wolferth	Jour. Am. Med. Assn., 1922, **79**, 1756	F	38	+	+	Typhoid	BPFA	+	2	D	Pyelonephritis.
8. Miller and Wolferth	Jour. Am. Med. Assn., 1922, **79**, 1756	F	30	+	+	Typhoid	BPFA	+	1	D	Pyelonephritis.
9. Wolferth and Miller	Appendix, this report 2502 (No. 9)	M	71	..	..	Pneumonia	BF	..	1	D	
10. Wolferth and Miller	Appendix, this report 4160 (No. 10)	F	..	..	..	Broncho-pneumonia	..	..	1	D	
11. Wolferth and Miller	Appendix, this report 6430 (No. 11)	M	..	..	..	Pneumonia; tuberculosis of lungs	..	..	3	D	
12. Wolferth and Miller	Appendix, this report 6702 (No. 12)	M	..	..	..	Acute malignant endocarditis	..	..	2	D	
13. Wolferth and Miller	Case IV, this report	F	72	0	0	Broncho-pneumonia	..	0	3	D	Diabetes and cardiac failure.

TABLE IX.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER OCCURRING IN PATIENTS WITH LESIONS OF THE CENTRAL NERVOUS SYSTEM.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Central nerve lesion.	Character of urine.	Exfoliation.	Depth of lesion.	Result.
1. Wilks . .	Trans. Path. Soc., London, 1863, **15**, 136	M	32	+	+	Acute paraplegia	..	+	2	D
2. Southam .	Med. Chron., Manchester, 1892, **17**, 230	M	28	+	+	Dislocated seventh cervical vertebra	BPFA	..	2	D
3. Cathelin .	Chir. urin. de Guerre, 1919, p. 88	M	21	+	+	Bulbar injury	F	+	1	D
4. Cathelin .	Chir. Urin. de Guerre, 1919, p. 88	M	29	+	+	Injury of fifth and sixth dorsal vertebræ	F	+	1	L
5 Esau . .	Ztschr. f. urol. Chir., 1921, **8**, 63	M	31	+	+	Wound of cord	BA	+	2	D
6. Wolferth and Miller	Appendix, this report 2469 (No. 1)	F	48	..	..	Hemiplegia tuberculosis; interstitial nephritis	B	..	1	D
7. Wolferth and Miller	Appendix, this report 3103 (No. 2)	F	..	..	..	Compression myelitis	..	..	1	D
8. Wolferth and Miller	Appendix, this report 3103 (No. 2)	M	..	..	..	Myelomeningitis	..	..	1	D
9. Wolferth .	Appendix, this report 6208 (No. 4)	M	..	..	..	Cerebrospinal	B	..	1	D
10. Wolferth and Miller	Case II, this report	M	67	+	+	Carcinoma of vertebræ and spinal cord	BAP	..	2	D
11. Wolferth and Miller	Case III, this report	F	47	+	+	Vertebra neoplasm with pressure on cord	P	..	3	D

TABLE X.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN WHICH TRAUMA SEEMED TO BE OF ETIOLOGICAL SIGNIFICANCE.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Trauma.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Liston*	Quoted from Pepin	M	70	+	..	Fall from scaffold	..	+	..	D	Cystotomy.
2. Pepin	Thésis, Paris, 1893	M	57	+	+	Rupture of urethra	BPF	+	3	D	Several perforations of bladder.
3. Fenwick	Brit. Med. Jour., 1910, **1**, 798	M	39	+	+	Fracture of pelvis	BPF	..	4	D	Complete destruction of bladder wall.
4. Perriol	Le Dauphine méd.,1912, **36**, 49	F	23	..	..	Fracture of pelvis with perforation of bladder	BF	+	3	L	

* Surgeons' Museum, London, Specimen No. 1933.

Miscellaneous.

TABLE XI.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN WHICH MISCELLANEOUS PREDISPOSING CAUSES WERE OPERATIVE.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Rouhault	Quoted from Pepin, Hist. de l'Acad. des sci. anat., 1714	M	..	+	+	..	+	2		
2. Tulpius	Observ. medicae, Lugduni Batavorum, 1716	F	..	..	..	B	+	1	L	
3. Boucher	Bull. Soc. anat. de Paris, 1841, **16**, 139	M	..	+	+	..	..	..	D	Bilateral inguinal hernia.
4. Lee	Trans. Path. Soc. London, 1863, **15**, 136	M	38	+	+	B	+	3	D	Abscess of scrotum.
5. Murchison	Trans. Path. Soc. London, 1868, **19**, 281	M	42	0	0	BF	+	1	D	Stone (?).
6. Schwarz	Centralbl. f. Gynäk., 1880, **4**, 121	..	..	..	..	..	..	..	D	Perforation of the bladder.
7. Orlowski	Centralbl. f. Chir., 1888, **15**, 855	F	3	+	+	BPF	+	1	L	Dysentery.
8. Clarke	Trans. Path. Soc. London, 1888, **39**, 164	M	36	+	+	BPFA	+	4	D	Perineal section; death from sepsis.
9. Falkenberg	Quoted from O'Neil, 1890	M	..	+	..	PF	+	..	L	Extravasation of urine.
10. Fenwick	Med. Soc. Trans., 1894, **17**, 346	M	52	..	..	..	+	3	L	Difficulty in urination twenty-five years.
11. Kelly	Operative Gynecology, 1898, p. 381	F	..	+	..	..	+	1	L	Followed ovariotomy; died a year later.
12. Legueu	Bull. Soc. anat. de Paris, 1898, **73**, 440	F	40	+	+	BPF	+	3	L	
13. Margulies	Quoted from O'Neil, Khirurgia, Moscow, 1904, **15**, 158	..	..	+	+	BFP	+	3	L	Etiology obscure.
14. Prigl	Ztschr. f. Urol., 1909, **3**, 163	M	54	+	+	BFA	..	1	D	Inserted pebbles in urethra.
15. Wolferth and Miller	Appendix, this report 7341 (No. 8)	F	35	..	..	..	..	1	D	Carcinoma of uterus secondary involvement of bladder.
16. Wolferth and Miller	Appendix, this report 857 (No. 5)	M	14	..	..	..	..	1	D	Appendicitis; peritonitis; fecal and vesical fistulæ.
17. Wolferth and Miller	Appendix, this report 1864 (No. 6)	M	..	..	..	..	..	1	D	Uremia; pyelonephritis right; hydronephrosis left.
18. Wolferth and Miller	Appendix, this report 2458 (No. 7)	M	69	..	..	B	..	3	D	Chronic interstitial nephritis.
19. Wolferth and Miller	Appendix, this report 6621 (No. 14)	F	..	..	..	..	..	1	D	Carcinoma of the vagina; bladder not involved.
20. Wolferth and Miller	Case V, this report	F	43	0	0	P	0	1	L	Cardiorenal disease.

TABLE XII.—AGES BY DECADES IN THE 105 CASES IN WHICH IT WAS RECORDED. YOUNGEST, THREE YEARS; OLDEST, SEVENTY-FIVE YEARS.

Age.	Total cases.		Cases without pregnancy.	
	Number.	Per cent.	Number.	Per cent.
1 to 10 years	1	0.9	1	1.6
11 to 20 "	10	9.5	7	10.9
21 to 30 "	33	31.4	17	26.6
31 to 40 "	38	36.2	17	26.5
41 to 50 "	10	9.6	9	14.1
51 to 60 "	4	3.8	4	6.2
61 to 70 "	5	4.8	5	7.9
71 to 80 "	4	3.8	4	6.2
Total	105	100.0	64	100.0

TABLE XIII.—SUMMARY OF DATA ON 153 CASES OF NECROSIS OR GANGRENE OF URINARY BLADDER.

Clinical conditions with which associated.	Number.	Male.	Female.	Retention.	No retention.	Catheterized.	Not catheterized.	Urine.				Exfoliation.	Depth of lesion.				Result.	
								Bloody.	Purulent.	Fetid.	Alkaline.		1.	2.	3.	4.	Died.	Lived.
1. Retropregnant uteri	40	0	40	40	0	11	2	22	13	21	13	32	10	5	6	10	25	14
2. Labor	21	0	21	15	..	14	1	13	7	9	7	20	6	5	5	1	5	16
3. External pressure	11	0	11	6	3	6	2	8	7	5	4	7	0	4	4	1	4	7
4. Cystitis	14	7	7	7	1	7	..	10	11	9	6	13	3	3	7	0	6	7
5. Stricture of urethra	7	7	0	6	..	1	..	3	2	5	5	6	1	2	2	0	6	1
6. Stone in bladder	6	5	1	4	..	3	..	2	5	3	2	6	1	2	1	0	1	4
7. Irritants	6	2	4	1	3	1	..	3	1	1	1	4	2	0	4	0	1	5
8. General infections	13	3	10	6	2	5	..	6	4	8	4	6	4	3	3	0	11	2
9. Gen. nerv. sys. lesion	11	8	3	7	..	7	..	5	3	3	3	4	6	4	0	0	10	1
10. Trauma	4	3	1	3	..	2	..	3	2	3	0	3	0	0	2	1	3	1
11. Miscellaneous	20	11	7	10	2	8	2	9	6	7	2	11	10	1	5	1	12	7
Total	153	46	105	105	11	63	7	84	61	74	47	112	43	29	39	14	84	65

Thus it will be seen that various etiological factors may be considered as operative in these groups of cases, but that no one stands out obviously as a possible cause for all. Retention had not occurred in all cases and it is impossible to assert that it was not secondary in many of those in which it did occur. Pressure from the outside on the neck of the bladder was present in only a minority of the cases. There is no evidence that irritants were injected into the bladder in any but the 6 cases of Table VII. It may be argued that the ammoniacal decomposition of retained urine was a sufficient irritant cause in many others, but the absence of retention in some of the cases would seem to eliminate this possibility. Though certain definite nerve lesions occurred only rarely, Cathelin[12] felt that all the cases could be explained on some

nervous influence, even a lethargic mental state, such as occurs in typhoid, being sufficient; but he surely was not familiar with the reports of cases in pregnant women, in men with prostatic hypertrophy and in those with local infections.

Infection seems to us to demand most serious consideration since this might have occurred in all the cases, either by introduction with a catheter, by operation or by blood stream. But it is impossible to prove that this always occurred, and on pathological grounds infection does not seem essential to the production of a simple necrosis of tissue. Such necrosis occurs not infrequently in other portions of the body from a mere interference with blood supply, as in an extremity. That a non-infectious necrosis of bladder tissue theoretically may occur cannot therefore be denied. That infection does occur in many of the cases, however, seems equally evident. Whether or not there are any specific organisms that especially lead to this condition cannot be asserted until many more studies have been made.

We are therefore inclined to believe, on the one hand, with Haultain,[1] both on experimental and clinical grounds, that mere interference with the local blood supply is a sufficient cause in some instances, especially when only necrosis occurs, and, on the other, with O'Neil,[2] that infection may explain some. In addition there is a small group of cases due primarily to the direct effect of chemical irritants injected into the bladder. The other assigned causes are probably operative in only a predisposing way, retention and pelvic masses acting only insofar as they obstruct the circulation, enlarged prostates and strictures leading to retention, and often to infection, and central nervous system lesions interfering with bladder evacuation and so producing venous stasis.

Thus we have been led to the conclusion that there are three primary factors which may produce bladder necrosis: Infection, circulatory stasis and chemical irritants, and that these may be operative either singly or combined. When necrosis goes on to gangrene infection is probably always present.

Under this heading a few words may be devoted to the age incidence. Table XII indicates that 67.6 per cent occurred in the third and fourth decades. It might be thought that this was due to the large number of cases in women incident to pregnancy, but excluding these it will be noted that still the majority of the cases (53.1 per cent) fall into this period of life. No period of life is immune, however, 1 case occurring in a child aged three years and 1 in a man aged seventy-five years.

Morbid Anatomy. *Gross Appearances.* In conditions having such diverse predisposing factors as the necrotic and gangrenous affections of the bladder, it is to be expected that great differences in morbid anatomy will be found. The appearances of the lesions

vary according to the duration, extent and severity of the involvement and the presence or absence of exfoliation.

The situation of the destructive process is practically always on the inner side of the bladder wall. Necrotic muscularis and serosa surrounding healthy mucosa and submucosa have not been described. If the outer coats are affected the inner coats are also affected, and in the latter the necrotic process is usually found in the more advanced stage. We have attempted to tabulate from the reports in the literature and our own material the depths

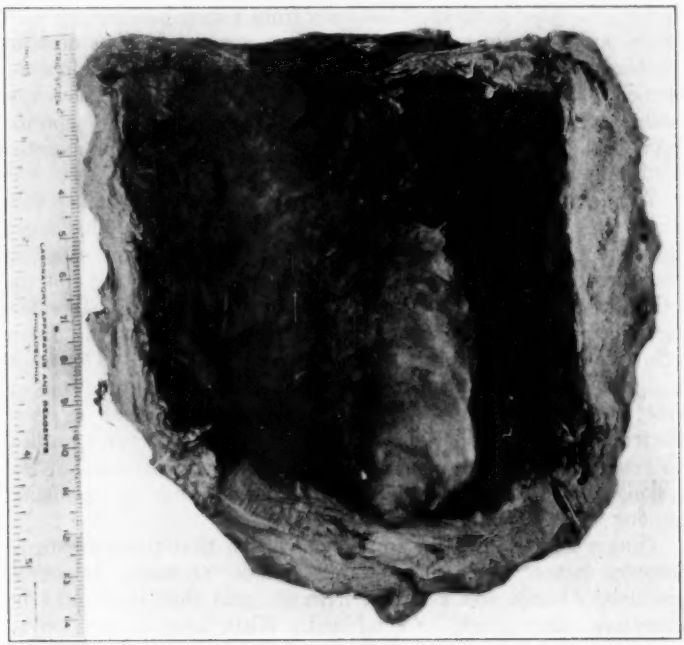

FIG. 1.—Photograph of interior of bladder showing widespread gangrenous involvement, which in places extended entirely through the greatly-thickened wall. There are present areas from which exfoliation has occurred. (Accession No. 141, Pathological Museum of the Philadelphia General Hospital. Courtesy of Dr. E. B. Krumbhaar.)

of the lesions. There are doubtless a number of faulty observations, but the figures may give some relative idea of the degree of bladder-wall involvement. In 43 cases the mucosa alone was said to have been affected; in 29 the submucosa also; in 39 the mucosa, submucosa and at least part of the muscularis; in 14 the entire thickness of the bladder wall was destroyed, either in a limited area or completely. Of the cases we report, in which microscopical

studies were made, the numbers in each group were 4, 5, 6 and 1, respectively.

The bladder is usually described as showing extensive necrosis or gangrene, but there are cases in which the extent of involvement is slight. One type is seen in the case reported by Dawson,[18] in which, after the injection of an irritant, large sheets of epithelium were exfoliated, and indeed in many the entire inner wall was affected. Another type is that seen in our Case IV and Case V, in which localized areas of bladder necrosis were found in patients who had died of apparently unrelated conditions. This type, we believe, as a result of examining a number of bladders and discussing the question with pathologists who have had large experience in necropsy work, is not so very uncommon as a terminal event. It probably has little pathological or clinical significance, except as evidence of terminal failure in the nutrition of bladder tissue.

In the cases with grave lesions, which group includes the great majority tabulated, the area of involvement is usually widespread. In the early stages the mucosa is greatly swollen and hyperemic, and may bleed so freely that it is difficult to clear the bladder for cystoscopical examination. Whitish patches of pseudomembrane may be present. The color of the mucosa quickly changes to dirty gray, greenish or black. The necrotic inner portion of the bladder in some cases is seen to be separated in places with rolling up of the edges. Finally exfoliation occurs and the surface of the bladder then assumes a rough shaggy appearance. Incrustation with urinary salts is sometimes seen. The bladder wall is usually greatly thickened, even after exfoliation.

Exfoliation of the necrotic tissue was observed in 112 of the 153 cases reviewed and probably would have occurred in all, had the patients lived long enough. The slough separated as small fragments, large sheets or as an entire cast of the bladder. Most common is the separation of one large mass and a number of small fragments. In females large fragments frequently have been passed *per urethram*, and in at least three instances this has occurred also in males. In several cases fragments have been removed or expelled through a cystotomy incision. Sometimes they have been found floating in the bladder at autopsy. They are extremely foul-smelling, dirty white, gray or greenish in color, friable, and often gritty due to deposits of urinary salts. Portions of bladder tissue may sometimes be recognized on microscopical examination, particularly muscle fiber, but in many cases the material is so decomposed that nothing can be recognized.

After the acute process in the bladder subsides repair may take place to an extraordinary degree. According to O'Neil,[2] if the peritoneum is exfoliated the surrounding organs take part in the repair and a secondary sac is formed by inflammatory adhesions,

which later become changed into fibrous tissue. In cases with exfoliation of almost the entire bladder such sacs have been formed. Where the exfoliation has been more superficial the bladder becomes covered over with tissue that on cystoscopical examination may be indistinguishable from normal mucosa. The bladder sometimes recovers its normal capacity, but in the cases with more severe involvement it is liable to remain greatly contracted and to become distorted in shape.

Microscopical Appearances. The characteristic finding on microscopical examination is a necrosis of the bladder tissues. The various coats involved may still be recognizable, or the process may have extended beyond this stage. There is usually a marked cellular infiltration, often with many red cells and fibrin in the necrotic area and in the zone separating it from healthy tissue. Bacteria in great numbers can usually be found. Not infrequently areas of pseudomembrane with a network of fibrin, white and red cells and bacteria are found over the surface of the bladder.

In the less acute cases the cellular infiltration may be principally of the round-cell type and beginning connective-tissue proliferation in the zone of demarcation may be seen. This was observed several times in the cases reported in the appendix.

Clinical Features. Diagnosis. Necrotic and even gangrenous lesions of the bladder arising during the course of profound illness may escape the notice of the attending physician. Of the 14 cases collected in the appendix, all of which were under observation in a hospital, the diagnosis was not arrived at in a single instance, and in but 5 was a diagnosis of any bladder lesion made. A patient in an obtunded state may have no bladder symptoms, or, if he does, may be unable to call attention to them. Under such circumstances, unless marked urinary retention occurs, no special interest is likely to be devoted to the bladder. Retention is usually a precursor of necrosis or gangrene, but may not develop until later in the course of the disease, few cases failing to show it at some stage. Even in the absence of retention, however, if the urine is examined or inspected frequently no cases except those with the mildest and most limited areas of beginning necrosis will fail to give unmistakable evidence of severe disease along the urinary tract.

The urinary findings, therefore, constitute a very important diagnostic feature. As the condition begins to develop, an excess of leukocytes or perhaps a slight hematuria is found. The urine later becomes fetid, in some instances the odor being almost unbearable. It is nearly always alkaline in reaction and usually contains varying amounts of blood, pus, debris and many bacteria. The presence of macroscopical amounts of blood in the urine and the fetor, both of which often occur early, should lead immediately to the suspicion of bladder gangrene. Fragments of gangrenous bladder tissue or mucopus may be present.

Other suggestive signs are interruption of the stream of urine during catheterization and inability to empty a full bladder by catheterization. The latter in some cases has been due to the fact that complete exfoliation of the mucosa had occurred and the exfoliated sac was filled with urine. Interruption of the flow of urine is usually due to the plugging of the catheter by exfoliated membrane or mucopus.

In a number of the more recent cases the diagnosis has been made or confirmed by cystoscopical examination. When available this is not only the most satisfactory method of determining the diagnosis, but also of discovering the extent of damage to the bladder.

If any of the exfoliated tissue is expelled or evacuated by catheter and, by microscopical examination, some element of bladder tissue is recognized the diagnosis is confirmed beyond question. In some instances, however, the extruded substance is so decomposed that no recognizable structure can be made out.

In the differential diagnosis the principal conditions to be considered are simple cystitis, pseudomembranous cystitis and tumors of the bladder. The presence of some affection graver than one of the ordinary forms of cystitis will rarely be suspected unless attention is drawn to such urinary characteristics as those described above. These should lead to careful search in the urine for exfoliated material, not merely exfoliated bladder epithelium, such as sometimes occurs in ordinary cystitis but fragments containing underlying bladder tissue. Since these are usually not found until late in the course of the disease cystoscopy must be relied upon for early diagnosis.

Much has been made of the distinction between pseudomembranous cystitis and necrosis or gangrene of the bladder, particularly in the French literature. Pseudomembrane formation occurs as a result of intense inflammation of the bladder and consists of deposits of exudate on the inner surface, made up principally of fibrin and cells. The pseudomembrane may exfoliate and in this respect resemble necrosis or gangrene. In a number of cases, in which only clinical findings were reported, the diagnosis of pseudomembranous cystitis was based solely on the fact that no bladder structure could be recognized in the exfoliated material. This does not constitute a valid basis for differentiation. As has been pointed out, in some cases with true bladder exfoliation the tissue is so disintegrated that no bladder structure can be recognized. Moreover, pseudomembrane may cover over necrotic bladder tissue or some parts of the bladder may be gangrenous and others covered over by pseudomembrane (as in Case I). It seems more in accord with the actual facts observed, therefore, to regard pseudomembranous cystitis not as a clinical entity to be differentiated from other forms of bladder disease, but rather as a form of inflammatory

reaction, which may occur during the course of intense cystitis and also in necrotic or gangrenous conditions.

Exceptionally a mistaken diagnosis of tumor of the bladder is made either on account of the urinary findings or the fact that bimanual examination discloses marked thickening of the wall. The clinical diagnosis of cancer was made in 2 of the cases reported in the appendix, and in 1 of these, after gross anatomical examination, the diagnosis was still adhered to, microscopical study being required to demonstrate its incorrectness. Also in Cases I and II this clinical diagnosis was made even after cystoscopical examination.

Usually there should be no difficulty in differentiating the two types of conditions, but occasionally there will be. In the absence of obvious predisposing factors to explain the onset of necrosis or gangrene, the possibility of underlying neoplasm naturally presents itself, and in some cases one may not be able to exclude malignancy by any of the methods of clinical study. Case I illustrates this point. The presence of gangrene of the bladder wall was clearly recognized on cystoscopy by Dr. Keene, but the thickness and induration of the bladder revealed by bimanual examination made him suspect the presence of cancer.

Complications. Gangrene of the bladder may be accompanied by general sepsis, but even cases with severe local disease may have no elevation of temperature or marked constitutional disturbance. Nephritis and uremia have occasionally been described as complications. Perforation of the bladder wall sometimes occurs and when it does the infected urine may escape into the general peritoneal cavity and set up a virulent peritonitis. The peritoneum is sometimes protected, however, by the formation of pericystic adhesions, even in cases where practically the entire bladder is exfoliated. In a few cases following perforation of the bladder extravasation of urine occurred about the genitalia, with the usual serious result of this condition. Infection of a kidney, such as pyelonephritis or pyonephrosis, was described in only 6 cases collected from the literature. We judge these complications to be far more frequent than is indicated by that figure as it was observed in 5 of the cases we report.

Prognosis. Of the 153 cases we have collected 65 lived, 84 died and in 4 the outcome was not stated. It would be fallacious, however, to estimate the mortality from these figures. A number of the cases (including those in the appendix) were collected from pathological material. It is unquestionable, furthermore, that many cases, particularly the milder ones, are overlooked entirely or regarded merely as simple cystitis. The mortality is greatly influenced by the type of morbid process which predisposes to the bladder lesion. Thus we find a very high mortality in those cases developing as a result of general infections, diseases of the central

nervous system and retrodisplaced pregnant uteri lodged in the pelvis. On the other hand, the mortality is comparatively low in cases developing during or after child-birth. The mortality is much higher in men than in women. Among 45 men, 12 lived and 33 died, while among 102 women, 52 lived and 50 died. This difference in mortality between the sexes is doubtless due largely to the easier drainage of the bladder through the urethra in women.

In the patients who lived, variable results as to recovery of bladder function were observed. In some there was complete or almost complete recovery. In the severe cases, however, there was usually definite limitation of bladder capacity and in several instances complete incontinence of urine.

Treatment. The fact that no cases of necrosis or gangrene of the bladder as complications of pregnancy and labor have been reported since 1893 (see Tables I and II) would seem to indicate that modern aseptic technic and the better general management of these conditions in modern times are important prophylactic measures. In general the avoidance of prolonged over-retention of urine, careful asepsis in catheterization, prevention of prolonged pressure against the bladder wall and promptness in the treatment of stone in the bladder, urethral stricture and enlarged prostate undoubtedly would lower the incidence of necrosis or gangrene. Rarely, in cases of severe general infection and in lesions of the central nervous system they appear to be unavoidable.

Very little is to be found in the literature concerning the actual management of these grave bladder lesions. In the vast majority of cases conservative methods of local treatment have been employed, such as frequent catheterization or constant drainage to avoid over-distention and irrigation of the bladder with normal salt solution, boric-acid solution or strong germicidal agents.

Haultain[1] stated that there could be little doubt that the result inevitably would be fatal in males unless the exfoliated sac were removed artificially. Later reports have shown, however, that exceptionally recovery has ensued after spontaneous expulsion of the slough *per urethram*. O'Neil[2] has affirmed that the results of operation in males have been excellent, but that the mortality is extremely high in non-operated cases. Analysis of the material now available substantiates O'Neil's statement. Cystotomy had been performed in 9 of the 12 males who recovered, and in only a few (3, possibly 1 or 2 more) of the 33 fatal cases. It should be pointed out, however, that in most cases the operation was done not on account of the bladder lesion alone, but because of the presence of some added factor, such as stone, urethral stricture or enlarged prostate. Thus the good results were doubtless contributed to by the removal of the causes of the bladder affections. Nevertheless, the present state of our knowledge would seem to warrant the statement that cystotomy should be undertaken in all

male patients in whom extensive necrotic or gangrenous bladder lesions have been discovered and in whom the general condition would justify such a procedure.

In females a more conservative position may be assumed with respect to operation on account of the fact that drainage through the short and dilatable urethra is much better than in males, and sloughs, even enormous ones, frequently have been expelled. It seems reasonable to suppose, however, that some of these cases whose progress was not satisfactory might have been benefited, although there is no satisfactory data to establish the fact, had cystotomy been done and better drainage secured. We believe that cystotomy should be given a trial under such circumstances.

Summary. 1. One hundred and fifty-three cases of necrosis or gangrene of the urinary bladder are reviewed, 21 of these (including 2 recently reported by us) being new ones.

2. It is suggested that the affection is not so rare as the scarcity of reports in the literature would indicate.

3. No single etiological factor can be determined at this time for all the cases, but either infection, circulatory disturbance or chemical irritants, or a combination of these factors, would seem to explain the causation in practically all instances.

4. The pathology and clinical features are reviewed.

5. It is suggested that cystotomy might be a justifiable and beneficial procedure in the more severe cases.

APPENDIX.

(*Abstracts of autopsy records of 14 cases exhibiting either necrosis or gangrene of the urinary bladder which were discovered in a review of 5250 autopsy protocols in the Pathological Laboratory of the University of Pennsylvania.—Courtesy of Dr. Allen J. Smith.*)

1. *Autopsy No. 2469.*—R. J., female, colored, aged forty-eight years; patient of Dr. Spiller at Philadelphia General Hospital. *Clinical diagnoses:* Hemiplegia; tuberculosis of the lungs and intestines; interstitial nephritis. *Gross findings* at autopsy (March 25, 1909): Extensive tuberculosis of the lungs, intestines and lymph glands; chronic abscess of the kidney (probably tuberculosis); pyelonephritis; amyloid infiltration of the spleen; gangrenous cystitis, the mucosa at the fundus being green-black and ulcerated. The contents of the bladder were cloudy and red. No *microscopical* report on bladder.

2. *Autopsy No. 3103.*—C. M., female, white, aged fifty years; service of Dr. Spiller at Philadelphia General Hospital. *Clinical diagnosis:* Compression myelitis, myocarditis and nephritis. *Gross findings* at autopsy (March 14, 1909): Bladder filled with greenish, purulent and granular material; bladder wall thickened;

mucosa of bladder greenish and shows distinct proliferation with dark and necrotic surface. *Microscopical report:* Muscle bundles fairly compact; submucosa the seat of connective-tissue overgrowth and small round-cell infiltration in circumscribed areas, over which the mucosa has disappeared; some free blood present on surface.

3. *Autopsy No. 4171.*—E. H., male, white, aged fifty-two years; patient at Philadelphia General Hospital. *Clinical diagnosis:* Myelomeningitis. *Gross findings* at autopsy (April 25, 1913): Urine purulent; inner bladder wall thick, edematous and black. *Microscopical findings:* Mucosa entirely missing, muscle bundles large and an increase of connective tissue in the muscular layer.

4. *Autopsy No. 6208.*—H. S., male; patient of Dr. Myers, Philadelphia General Hospital. *Clinical diagnosis:* Cerebrospinal disease and ulcerative cystitis. *Gross findings* at autopsy (September 12, 1919): Right pyonephritis; brownish, bloody fluid in the bladder; wall of bladder overlaid with necrotic grayish-yellow membrane; when membrane was scraped off a slaty color remained (diagnosed acute necrotic cystitis). *Microscopical findings:* Entire bladder wall edematous; mucosa entirely replaced by a process of necrosis, with infiltration of small round and polymorphonuclear cells, this process involving the deeper layers as well. Over the necrotic mucosa was a fibrinous exudate.

5. *Autopsy No. 857.*—F. S., male, aged fourteen years; patient of Dr. Edward Martin at University Hospital. *Clinical diagnoses:* Appendicitis, peritonitis, fecal fistula, secondary vesical fistula, *Gross findings* at autopsy (February 27, 1906): Bladder wall somewhat thickened; mucous membrane of the bladder was a mass of necrotic areas alternating with areas containing thick blackish-green diphtheritic membrane; there was an opening at the fundus into the inflammatory mass in left groin and so to fecal fistula. No *microscopical report* on the bladder tissue.

6. *Autopsy No. 1864.*—W. M., colored; patient at University Hospital. *Clinical diagnosis:* Uremia. *Gross findings* at autopsy (December 18, 1907): Gangrenous cystitis with areas of black discoloration and calcareous deposits, urethritis; right pyelonephritis and left hydronephrosis. The bladder contained viscid deep-red fluid. The wall was much thickened, there being great profusion of rugæ over the mucous surface. The mucosa was deep red in color with spots of black. To palpation there was a distinct grittiness, suggesting mineral material. Urethral submucosa exposed in places. *Microscopical findings:* Loss of mucous membrane of the bladder, the inner surface of bladder being covered by mass of loose fibrous tissue containing leukocytes and plasma cells. Some calcification present.

7. *Autopsy No. 2458.*—W. P., male, white, aged sixty-nine years; patient of Dr. Christian at Philadelphia General Hospital. *Clinical diagnoses:* Epithelioma of the bladder and chronic interstitial

nephritis. *Gross diagnoses* at autopsy (March 22, 1909): Scirrhous carcinoma of the bladder, gangrenous cystitis and ascending pyelonephrosis Bladder was dilated and contained dark-red, cloudy fluid. Numerous nodular areas were observed and these seemed to infiltrate the muscle and surrounding areas. The inner surface of bladder wall was gray and black in color. *Microscopical findings:* Mucosa and submucosa missing, muscular layer (inner part) necrotic. No signs of carcinoma.

8. *Autopsy No. 7341.*—P. F., female, aged thirty-five years. *Clinical diagnosis:* Carcinoma of uterus with secondary anemia. *Gross findings* at autopsy (September 12, 1921): Small ovarian cyst adherent to bladder; soft gangrenous mass in lower portion of uterus; bladder greatly thickened and inner surface covered with white material; carcinoma at inferior portion of bladder (specimen in Museum). *Microscopical findings:* Acute necrotic cystitis; carcinoma, primary in uterus.

9. *Autopsy No. 2502.*—W. P., male, white, aged seventy-one years; patient of Dr. William Hughes in Philadelphia General Hospital. *Clinical diagnosis:* Croupous pneumonia, cancer of the liver, chronic interstitial nephritis and myocarditis. *Gross diagnoses and findings* at autopsy (April 10, 1909): Croupous pneupneumonia, chronic interstitial nephritis, cirrhosis of the liver, obstruction of common bile duct and gangrenous cystitis. The bladder contained cloudy, red-black, foul-smelling urine. The mucosa was green-black and covered with opaque white material. No *microscopical report* on bladder tissue.

10. *Autopsy No. 4160.*—E. H., female, white, aged seventy-six years; patient at Philadelphia General Hospital. *Clinical diagnoses:* Myocarditis and carcinoma of the bladder. *Gross findings* at autopsy (April 18, 1913): Exudation over the inner bladder wall and black spots. *Microscopical findings:* Mucosa entirely missing, submucosa thickened, muscularis thickened and infiltrated with fibrous tissue and round cells. No evidence of carcinoma.

11. *Autopsy No. 6430.*—J. L., male; patient of Dr. Morgan at Philadelphia General Hospital. *Clinical diagnoses:* Chronic ulcerative pulmonary tuberculosis and miliary tuberculosis. *Gross findings* at autopsy (February 14, 1920): Diffuse and extensive ulceration of the bladder (possibly tuberculous). *Microscopical findings:* Mucosa replaced by a necrotic mass, this extending into the muscular layer. The muscle coats were edematous and some muscle fibers were swollen and broken with an increase of fibrous tissue between the bundles and exudation of leukocytes and lymphocytes. The serosa was fibrosed, edematous and ragged.

12. *Autopsy No. 6702.*—K., male. *Clinical diagnosis:* Old cardiac disease and acute malignant endocarditis. *Gross findings* at autopsy: Bladder showed patches of superficial ulceration overlaid by dirty yellow, adherent membrane with granular mineral

deposits. Thick turbid material covered the entire inner surface. *Microscopical findings:* Subepithelial parts showed hemorrhagic in some places, edematous in others and necrotic in still others. In certain areas mucosa was absent and the submucosa necrotic. The sloughing membrane consisted of highly disintegrated leukocytes, bacteria and necrotic tissue.

13. *Autopsy No. 4425.*—C. H., male, colored, aged forty-eight years; patient at Philadelphia General Hospital. *Clinical diagnoses:* Endocarditis, cystitis and enlarged prostate. *Gross findings* at autopsy (March 2, 1914): Chronic catarrhal cystitis with phosphatic incrustations; foul-smelling chocolate-brown urine; inner surface of bladder encrusted with gritty white material and irregular areas of brownish-red material. *Microscopical findings:* No mucosa or submucosa; superficial parts necrotic; muscular coats separated by broad bands of old fibrous tissue and masses of red blood cells; on mucosal side the muscularis extremely infiltrated by erythrocytes and muscular fibers were granular and the nuclei fragmented and shrunken. The most superficial parts were entirely necrotic.

14. *Autopsy No. 6621.*—M. U., female; patient of Dr. Joseph Sailor at Philadelphia General Hospital. *Clinical diagnoses:* Chronic myocarditis and cystitis. *Gross findings and diagnoses* at autopsy (May 15, 1920): Carcinoma of upper vagina; bladder not involved, but left ureter blocked by a firm nodule. The inner bladder wall was bright red with a few grayish dirty areas. *Microscopical findings:* No carcinoma of the bladder, but the mucosa was necrotic.

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10. See Table VIII, No. 1.
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12. See Table IX, No. 3.
13. See Table X, No. 2.
14. See Table IV, No. 12.
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MEDICAL BILIARY DRAINAGE.

By A. Sachs, M.D., M. C. Howard, M.D.,
AND
M. W. Barry, M.A.,
OMAHA, NEB.

(From the Department of Medicine, Creighton University, Omaha, Neb.)

The literature has contained many interesting articles on this timely subject during the past four years, and directly opposite views exist as to its real value. Some consider it a valuable diagnostic aid in differentiating lesions of the upper right quadrant, and also an excellent therapeutic adjunct in the treatment of biliary disease, while others claim that it has very little value, and question its reliability.

The extremist on any subject is usually wrong, as is also the pessimist. If any subject is to be brought before the medical profession forcibly, it usually requires an enthusiast to do so. This Lyon has accomplished, and he deserves credit not only for arousing new interest in biliary disease, but also in opening the way for new physiological and chemical investigations.

Since our last publication on biliary drainage, in May, 1921, we have continued our work, constantly striving to arrive at the truth in an unprejudiced and scientific manner, and it is with this end in view that we offer this publication. We have continued our conservative view-point and while not being able to agree with all facts, believe that it undoubtedly has some value as a diagnostic and therapeutic agent.

Some of the greatly disputed points are as follows:

1. Does the gall-bladder contract?
2. Does the gall-bladder empty by a definite reflex of sphincter relaxation and gall-bladder contraction?
3. Are there other factors which assist the gall-bladder in expelling part of its contents?
4. Is the gall-bladder a mere reservoir, or has it definite function?
5. Is "B" bile gall-bladder bile?
6. Is there a chemical change which can account for the dark or "B" bile, or in other words, an oxidation of pigments?
7. Is all dark colored bile "B" bile?
8. Does magnesium sulphate have specific action, or can other substances likewise cause sphincter relaxation?
9. Is medical biliary drainage of any aid diagnostically?
10. Is medical biliary drainage of any value as a therapeutic procedure?

11. In what manner is biliary drainage of value and would gastric lavage afford as much relief as biliary drainage?

It is not the purpose of this paper to give detailed anatomical and physiological descriptions of the organs under consideration, yet it is well to review just one or two points. The gall-bladder has a capacity of about 50 cc. Its walls consist of fibro-elastic tissue, and unstriped muscle fibers, which are longitudinal, circular and oblique. The common bile duct is guarded by a sphincter called the sphincter of Oddi. It is conceded by most men that this is a definite sphincter and has sphincteric action. It was first described by Oddi in 1887, confirmed by Hendrickson in 1898, also by many other observers since then.

It is by the tonus of this sphincter that the bile is reverted into the gall-bladder, and through its relaxation that the bile is permitted to flow into the duodenum. The flow of bile in a normal dog is intermittent, and occurs in spurts; however, on removal of the gall-bladder its flow becomes more continuous. There are certain species of animals that do not possess a gall-bladder, in which the flow of bile is continuous, namely the horse, the deer, the rat, and the pocket gopher. The sphincter of Oddi in this species is histologically the same as those with a gall-bladder.

Judd and Mann have found that in a normal anesthetized dog the sphincter of Oddi will resist about 150 mm. of water pressure before being relaxed. However, after the removal of the gall-bladder, the sphincter resistance was lowered and it required only 40 mm. of water pressure for its relaxation. In animals without a gall-bladder, the sphincter resistance is also low, being from 30 to 70 mm. of water, hence the continuous flow of bile in this species.

Johnson has demonstrated that the duration of sphincter relaxation varied according to the nervous state of an animal. He frightened dogs and bile ceased to flow, however, on the same dogs, while sleeping, a continuous flow for one hour and a quarter was noted. This observation can be corroborated in humans, for oftentimes during the first medical drainage no free drainage of bile is obtained, even though the tube is in its proper place and the duodenum is douched several times with magnesium sulphate. On the second and third drainages the patient's fear has vanished, and better drainages are obtained.

It is a well known fact that gastric chyme rich in fats, proteoses and peptones cause an excessive secretion of bile, because it is needed for their digestion. Carbohydrates on the other hand call forth very little secretion of bile, but a large amount of pancreatic secretion.

All patients do not have the same stature. Some have a wide epigastric angle, and others a narrow one. This immediately informs us that the relationship of liver, gall-bladder, bile ducts,

and duodenum, are not the same in all individuals, hence it must be borne in mind that some gall-bladders and cystic ducts are joined at a more acute angle than others. Graham in his experiments on dogs has demonstrated that position or gravity was a factor in expulsion of dye injected into the gall-bladder. This fact will be taken up more in detail at a later time.

The valves of Heister are not always arranged the same in cystic ducts. Occasionally an anomaly of these valves or folds act as an obstruction making it difficult to empty manually a gall-bladder, however, these same gall-bladders can be emptied more readily if they are pulled more or less taut. Barker believes these valves to be under sympathetic control and act to as a protection to the inflow of bile. They are unquestionably placed there for a definite purpose, hence it seems logical that they may at times act as a hindrance to the outflow as well as to the inflow of bile, which is a fact worth considering before diagnosing obstructions of the cystic duct.

The technic of passing the duodenal tube, preparation of the patient, etc., has been given in numerous publications, and need not be again repeated. However, it might not be amiss to state that we feel that laborious washing with permanganate, lavoris, and other antiseptics are unnecessary, as has been demonstrated by our bacteriological studies, and confirmed by Smithies. Also, Escherich, Hess and McNeal and Chase all found that the normal fasting duodenum is usually free from organisms. Astringents themselves may be irritant, and occasionally produce a duodenitis. Careful and frequent lavaging will cleanse the stomach and duodenum in just as efficient a manner for all purposes, as the use of antiseptics and astringents.

One point which is brought out by Lyon and bears especial emphasis, is the slow feeding of the last 20 cm. of the duodenal tube, for it is in this last procedure that curling of the tube in the stomach so frequently occurs.

1. Does the Gall-bladder Contract?

The gall-bladder possesses circular muscle fibers which were placed there for some purpose, and the most logical one is that they were necessary for gall-bladder contraction. In 1894 Doyon carefully studied the innervation of the gall-bladder and bile ducts. In 1905, just eleven years later, Bainbridge and Dale covered the same ground, and although they disagree as to the effect produced by splanchnic stimulation, both recorded gall-bladder contraction. From the elaborate experiments of Bainbridge and Dale, one can readily see the difficulties encountered in registering actual gall-bladder contraction. Contractions of the abdominal viscera, activity of adjacent contractile organs, changes in the volume of the liver, may also record rises in gall-bladder pressure, simulating gall-bladder contraction. However, by their careful technic, they

were able to overcome these difficulties. In one of their experiments with adrenalin, they visualized small waves of contraction.

Okada also recorded rhythmic contractions of the gall-bladder and found the contractions were increased after a meal of meat. W. A. Johnson noted a minute wave of contraction in the gall-bladders of two dogs operated under local anesthesia. The contractions were very small and were at no time of sufficient force to empty the gall-bladder, a point of great importance, and which will be discussed later.

Freese also recorded gall-bladder contractions and measured the contractile force, finding that the maximum force of its contraction did not materially exceed the maximum secretion pressure of bile.

Crohn, Reiss and Radin, in experiments on dogs, report that they were unable to note any gall-bladder contraction. They also report that the sphincter (Oddi) while capable of contractility and closure under mechanical or faradic stimulation, acted normally very little as a sphincter. The flow of bile was continuous, not interrupted or rhythmic, and no functional use of the sphincter muscle was observed. On strong faradic stimulation of peripheral end of the right vagus, they noted general abdominal contraction of intestines, diaphragm and stomach, and with these contractions, the expulsion of blue colored bile was observed, the gall-bladder having previously been injected with a methylene blue solution so as to recognize bladder bile.

Gall-bladder contractions are difficult to visualize, and if definitely recorded and seen by others, it is difficult to believe they do not exist. The maximal contractile force is only slightly over that of liver secretion pressure, hence, it is easy to understand why gall-bladder contractions may be overlooked.

Another favorite argument is that no surgeon has ever seen gall-bladder contraction. Some individuals have the erroneous idea that the gall-bladder forcibly contracts and immediately expels all of its contents. However, this does not take place, for only minute spurts of bile occur, and the gall-bladder never completely empties itself. When the gall-bladder is not distended, it is flaccid, and not in the state of contraction.

That gall-bladder contractions exist can hardly be questioned. However, the contraction force being so minimal, it is hard to believe that it alone can account for expulsion of gall-bladder contents, and in our opinion, it is only one of the factors which assist in this process.

2. Does the Gall-bladder Empty by a Definite Reflex of Sphincter Relaxation and Gall-bladder Contraction?

Meltzer, in 1917, described the law of contrary innervation, and compared the gall-bladder with its sphincter to the urinary bladder and its sphincter. He cites the experiments of Rost,

who found that the injection of peptone and albuminoses through a duodenal fistula of a dog, was followed by an immediate discharge of bile, and he believed the same was produced by a reflex act causing a relaxation of the duct sphincter, and simultaneously a contraction of the gall-bladder. From the foregoing and other experiments, Meltzer believed that the gall-bladder and its sphincter were regulated by a definite reflex mechanism dominated by the law of contrary innervation.

Bainbridge and Dale saw no reflex contraction of the gall-bladder with relaxation of the sphincter, either by electrical stimulation or application of 0.4 per cent HCl. Their experiments were performed under anesthesia, and hence these authors state that this was no evidence as proof against the law of contrary innervation.

Okada found at times a distinct increased gall-bladder contraction by administration of 0.4 per cent HCl, and also with olive oil, not constant enough however, to draw definite conclusions.

A point in favor of Meltzer's law is an experiment by Judd and Mann previously reported in this paper, namely, that in a normal dog, the sphincter resistance is 100 to 150 mm. of water pressure. In dogs with the gall-bladder removed, the sphincter resistance drops to 40 mm. water pressure, and the ducts dilate. The only logical explanation of this lessened sphincter resistance and duct dilatation after removal of the gall-bladder must be through some disturbance produced by injury to the nervous mechanism controlling the relationship between the gall-bladder and duct sphincter. In animals without a gall-bladder, duct resistance is also lower than in those with a gall-bladder.

Harer, Hargus and van Meter believe this lessening of pressure by gall-bladder removal depends to a certain extent on the development of the muscle of the duct sphincter, because Rost found that after cholecystectomy, dogs may be divided into two groups; one group with well developed sphincter muscles continued to discharge bile into the duodenum intermittently until the common duct and ampulla became so widely dilated as to paralyze the muscle of Oddi. In other dogs, with poorly developed sphincter muscles, the bile was discharged continuously, and there was no dilatation of ducts. Sphincter development is important but cannot entirely explain the above, because Judd and Mann found a drop in sphincter resistance after gall-bladder removal, even though the duct sphincter was well developed, as evidenced by duct dilatation.

Clinically and experimentally, one may get sphincter relaxation without apparent expulsion of gall-bladder contents. Anyone having made use of medical biliary drainage has noted only one type of bile may be aspirated after repeated instillations of magnesium sulphate, even though the gall-bladder is intact and apparently normal. This cannot be used as an argument for or against the law of contrary innervation, because on one day a poor drainage

may occur and then several days later, in the same patient, all types of bile may be recovered.

Several men also report that in dogs in which the gall-bladder is injected with a dye so as to determine bladder bile, no dye was recovered after instillation of magnesium sulphate, HCl, peptone, etc.

In our experiments on decerebrated dogs we were able at times to recover spurts of dye by instillation of magnesium sulphate into the duodenum, and at times no dye was recovered. These experiments were not performed to prove or disprove the law of contrary innervation because no attention was paid to respiration, contraction of neighboring organs, etc. It is only mentioned here to show that no dye being recovered is no argument for or against the law of contrary innervation.

While it is logical to assume that the law of contrary innervation holds true as regards the gall-bladder and its sphincter, definite scientific proof is lacking, and more work is needed to prove this valuable hypothesis.

3. Are There Other Factors Which Assist the Gall-bladder in Expelling Part of its Contents?

From the experiments of Freese and others as stated before, the contractile force is minimal and it seems doubtful if this factor alone can account for the expulsion of bile from the gall-bladder.

The experiments of Bainbridge and Dale definitely show that the contraction of the abdominal muscles and diaphragm, changes in the volume and turgescence of the liver, the activity of adjacent contractile viscera could all record increase in gall-bladder pressure, and hence in humans may be a factor in gall-bladder expulsion.

Johnson has definitely shown that the intermittent flow of bile bears a definite relation to respiration and that inspiration is undoubtedly a factor which aids gall-bladder expulsion. This can also be observed clinically; if, during a biliary drainage the bile flow commences to lessen, and then the patient is instructed to take several deep breaths, the flow is again resumed. Graham has verified Johnson's findings and demonstrated that position or gravity is also a factor in aiding the expulsion of injected dye from the gall-bladder of dogs. However, in human beings in the sitting or standing posture, the gall-bladder is usually lower than the cystic duct, and hence gravity cannot materially aid in its emptying process.

Harer *et al.* quote J. E. Sweet, who believes that the gall-bladder is emptied of its contents or part of its contents by pressure of the congested liver and the distended stomach during digestion, and by the milking action of the peristaltic waves as they pass down the duodenum. As the waves progress they act on the intramural portion of the common bile duct, just as the hand of the milkmaid acts on the teat in milking a cow. A slight negative pressure is

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set up in the common duct and the bile flows into the duodenum. The valves of Heister are so constructed as to assist the entrance of bile into the gall-bladder, but once there, they make its withdrawal more difficult. Sweet therefore concludes that the only logical explanation of emptying the gall-bladder is by means of pressure from adjacent distended and congested organs, and by the milking action of the duodenal peristaltic waves.

Werelius believes that the gall-bladder has a suction bulb action similar to a stomach tube with its bulb.

The normal gall-bladder wall possesses a certain amount of elasticity or tone and when the sphincter is relaxed, this same elasticity or tone may also be a factor which aids the gall-bladder in emptying part of its contents. It is agreed by all that forceful contraction does not occur, and as we have reported in a previous article, it appears to be more of a collapse than a contraction.

Syphonage may be an added factor which aids the other expelling agents in medical biliary drainage. The sphincter being relaxed by HCl, peptone, magnesium sulphate, or other salts, and the bile flow started, it is logical to assume that syphonage may materially aid the other expelling forces.

From the various theories reported it seems most probable that no one factor is responsible for the gall-bladder expulsion, but rather a combination of several and perhaps the least important of all is gall-bladder contraction.

4. Is the Gall-bladder a Mere Reservoir, or Has It Definite Function?

The function of the gall-bladder has long been a disputed question, and a diversity of opinion still exists as to its real function.

A cholecystectomy may be performed and the patient remains in apparent health for years. This has led many to believe that the gall-bladder has no essential function. This fact alone is not sufficient proof, inasmuch as Nature compensates for the loss of any organ, and this is likewise true with the gall-bladder, for when it is removed the ducts dilate, which is Nature's method toward compensation for its loss.

In animals that have no gall-bladder, the ducts are larger, which again may be Nature's method of compensating for the absence of a gall-bladder.

Rous and McMaster have experimentally proven that the gall-bladder has a definite concentrating function and is able to concentrate bile ten fold. They have also demonstrated that as long as the gall-bladder or part of the cystic duct was left, pigmented bile was present; however, if these structures were removed in their entirety, no pigmented bile was present and only the so-called white bile of surgeons was found. They likewise found that the gall-bladder secreted more mucus per surface area than any other organ, and also that it secreted considerably more mucus than the bile ducts.

The normal or static gall-bladder always contains darker pigmented bile than the liver or bile ducts. Fitz found that gall-bladder bile from cases having cholecystitis with stones, was less pigmented than those without stones. This is not a fast rule, for in some cases of cholecystitis with static bile and soft stones, dark pigmented bile is present. The concentration of bile can hardly explain this change, hence we must otherwise account for the oxidation of these pigments. It is claimed by some that an oxidase is present in the gall-bladder, hence an oxidation of bilirubin to biliverdin. Fitz reported that gall-bladder bile was acid and not alkaline, as has been generally accepted by most men. We have found in test-tube experiments that if alkalies are added to yellow ox bile, they remain yellow; if however, graded quantities of dilute hydrochloric acid was added, it became green more readily as the concentration of acid advanced. It was noted that specimens with a pH of 6.4 or less invariably became green on standing, while those with a pH higher than 6.4 remained yellow. (This point will again be discussed under "B" bile.) The acidity of bile undoubtedly aids in its oxidation. However, it does not fully explain all dark biles, and we are at present working on this problem.

It is supposed by some men that the mucus of the gall-bladder might be a factor in the oxidation of pigments. However, proof is still lacking. Some claim that it is merely a reservoir for the storage of bile. Others claim that it is a mere buffer in the circulation of bile, equalizes its pressure and protects the pancreas.

It seems logical that the gall-bladder may equalize pressure in the biliary system; however, that it is needed for protection of the pancreas does not seem probable, as demonstrated by recent work of F. C. Mann and Giordano on the bile as a factor in pancreatitis. In this article they state that the number of instances in which the anatomical arrangement, in the relationship of the common duct to the pancreatic duct, that would permit bile to pass into the pancreatic duct, is very small. They also found that the percentage of instances where mechanical obstruction or action of the sphincter muscle that would convert the two ducts into a continuous channel was very small, and concluded that the reflux of bile as a factor in the production of pancreatitis is minimal so that we must look elsewhere for the cause in most cases of pancreatitis.

The gall-bladder with its concentrating function, is in part a storage chamber. Thirty cubic centimeters per hour is the average amount of bile secreted, which may be increased or decreased according to the amount and kind of stimulation present. Four hundred and twenty cubic centimeters are secreted in the interval between digestion and this being concentrated ten times, can readily be stored in the gall-bladder.

Leeds believes the gall-bladder adds a hormone which increases bile formation.

In the past it was believed by some that the gall-bladder possessed a hormone which stimulated HCl secretion. However, this is not borne out clinically. In studying 100 operative cases of gall-bladder disease in which a gastric analysis preceded the operation, no definite conclusion could be arrived at concerning hyper- or hypo-acidity, with reference to the cholelithiasis or cholecystitis. It is true that acid values are lower in some cholecystectomized patients, however, no conclusion can be drawn from the same, because gastric acidity is a variable factor, and no rule can be applied to it.

Although much progress has been made as regards gall-bladder function, continued experimentation is needed to determine what other part it plays in the biliary system, and what harm, if any, occurs from its removal.

5. Is "B" Bile Gall-bladder Bile?

A greatly disputed point among men interested in medical biliary drainage, is whether the dark bile called "B" bile is in reality gall-bladder bile.

Lyon originally separated his aspirations into three types of bile, "A" bile, duct bile; "B" bile, gall-bladder bile; "C" bile, liver bile. This naturally was merely an arbitrary division and not meant to be construed literally.

This division largely depends on a color change and microscopical sediments, hence there naturally must be a mixture of various types of bile in all specimens. "A" bile is never just duct bile, but a mixture of duct bile and liver bile, and likewise "B" bile is never just gall-bladder bile, but a mixture of liver bile and gall-bladder bile. The gall-bladder never empties itself completely, and usually sends out small spurts of bile. The amount expelled by the gall-bladder varies greatly and depends entirely on the force exerted on it, or by it. The "B" fraction is never wholly gall-bladder bile, and represents only the gall-bladder fraction, or in other words, that part of the drainage which contains some of the gall-bladder bile or elements.

If 1 cc of ink is added to 20 cc of water, the mixture is naturally a dark colored fluid, if 4 cc of ink are added to the above amount of water, the mixture is a darker one, and so it is in all probability with "B" bile, that is, "B" bile being a mixture of gall-bladder bile and liver bile.

In reading color changes, no two laboratories agree, and for that reason interpretations of "B" bile will necessarily be a variable factor. "B" bile should not only be dark but likewise have the qualities of "B" bile, namely increased mucus, cholesterin crystals, pigmented columnar cells, etc. Color changes must be observed through the glass window in the duodenal tube, and not taken after the bile has been standing, because it is a well known fact that bile pigments oxidize when exposed to light and air.

In some cases of medical biliary drainage, the duodenal tip will itself produce a relaxation of the sphincter of Oddi, and three types of bile can be obtained. No chemical agent being used, the darker or "B" bile in all probability represents the gall-bladder fraction, because it is in the gall-bladder that the darker pigment is found. Meyer and Einhorn were the first to use this method, and regard that duodenal contents in fasting cases are of great value in biliary diagnosis.

Gall-bladder bile is undoubtedly used for digestion, hence the gall-bladder must empty part of its contents at some time during digestion. It is easy to prove that gall-bladder contents reach the intestine, hence it seems logical to suppose that a part of it can be obtained in a biliary drainage.

Experiment I. September 16, 1922. A white male dog, weighing 18 pounds, anesthetized with ether at 9.45 A.M. Abdomen opened under aseptic conditions at 10.00 A.M. and 4 cc of carmine dye were injected into the gall-bladder. Abdomen closed. At 12.30 P.M. dog was up and about and in excellent condition. No food given this day, but water *ad lib.* September 17, 1922, there was evidence of several bowel movements during the night, but no dye was detected. A feeding of beef, chicken bones, and bread was given, which he ate readily. September 18, 1922, there were new stools of hardened consistency which contained a reddish pigment. The dog was now killed by a massive dose of strychnine (intracardially).

Autopsy. Abdomen opened. Gall-bladder more reddened than normal. Gall-bladder still contained considerable dye and bile, about 6 cc. Stomach empty, duodenum empty. No stain about ampulla. At a distance of 24 cm. distally, the dye was mixed with the fluid contents of the bowel. This continued into the large bowel. Several pieces of inspissated feces taken from rectum showed our dye intermixed with the same.

Conclusion. Dye found in feces forty-eight hours after its injection into the gall-bladder showing that part of the gall-bladder contents are expelled sometime during digestion.

A number of men have injected dye into the gall-bladder of dogs and tried to recover the same by douching the duodenum with magnesium sulphate.

Crohn *et al,* report that they were unable to recover the dye in their dog experiments except in one. In this experiment the dye was obtained only after faradic stimulation of the peripheral end of the right vagus, which caused general contractions of the abdomen, stomach and intestines. However, this shows that gall-bladder bile can be obtained whether it be by external factors, gall-bladder contraction, or a combination of both.

Johnson of Cleveland, in dog experiments, obtained three types of bile in normal dogs, and not in cholecystectomized dogs.

Graham, in dog experiments, was able to recover dye injected into the gall-bladder of dogs when position or gravity was used, and concludes that the so-called "B" fraction in non-surgical biliary drainage, is in part, at least derived by gravity from the gall-bladder.

Welch, *et al.*, of Lincoln, reports an experiment in which they recovered the dye from the gall-bladder of a dog, by use of magnesium sulphate.

In our own experiments, we were able to recover the dye injected into the gall-bladder in three instances. We used decerebrated dogs because in this manner anesthesia was eliminated and we were dealing with a living automaton.

Experiment II. Black female dog, ether anesthesia at 12.30 P.M. Carotids tied at 12.48 P.M. Decerebrated at 1.00 P.M. Dog in good condition at 1.30 P.M. Abdomen now carefully opened and tube passed per orum into stomach, then into duodenum and sutured at 2.15 P.M.; 5 cc of neutral red solution injected into gall-bladder. At 2.20 P.M., 25 cc warm magnesium sulphate injected into duodenum through duodenal tube. This returns light yellow. At 2.25 P.M., fluid assuming a reddish color; at 2.30 P.M., fluid deep red; at 2.46 P.M., fluid still red; at 3.05 P.M., fluid still red; at 3.15 P.M., fainter red. Carotid pressure registering 100 mm. of Hg. At 3.30 P.M., 15 cc of magnesium sulphate again injected obtaining a light yellow fluid. No further evidence of dye followed.

Autopsy (at 4.00 P.M.). First portion of duodenum unstained. Beginning about 2 cm. above ampulla, the mucosa was markedly red and stained for a distance of 115 cm. distally with a bright red color. Gall-bladder not empty; 8 cc of bile intermixed with dye still present.

Conclusion. Spurts of gall-bladder bile do occur. Gall-bladder does not completely empty.

Experiment III. A tanned mongrel, weighing 63 pounds. Ether anesthesia at 11.00 A.M. Carotids tied at 11.30 A.M. Decerebrated at 12.00 M. Abdomen opened at 12.30 P.M. Dog in good condition. Duodenal tube passed and tip sutured just beyond pars pylorica. Gall-bladder distended. Four cc of dye injected into gall-bladder at 1.15 P.M. At 1.20 P.M., jejunum opened and no dye present. At 1.25 P.M., 33 cc of 33 per cent magnesium sulphate injected through duodenal tube; 10 cc syphoned out. Jejunum closed by sutures and abdomen carefully closed. Drainage poor on account of high position of duodenal tip. At 2.45 P.M., abdomen was opened, and no marked change in size of gall-bladder found. Dog killed by gas.

Autopsy. Stomach and first portion of duodenum unstained. Ampulla deeply stained, and for some distance distal to it.

Conclusion. The tube was placed too high, and a poor drainage resulted. The dye was present at ampulla and distal to it, showing that at least some dye was expelled but gall-bladder not empty.

Experiment IV. Black female dog, weighing 60 pounds. Anesthetized 10.45 A.M. Carotids tied 11.10 A.M. Decerebrated 11.25 A.M. Dog in good condition 11.40 A.M. Abdomen opened 11.45 A.M., and duodenal tube passed in usual manner. Gall-bladder distended. Dye injected into gall-bladder, and abdomen carefully closed. At 11.50 A.M., duodenum douched with 20 cc warm water, returned bile stained; 12.10 P.M. drainage still light yellow; 12.15 P.M., 30 cc of warm 33 per cent magnesium sulphate injected; 12.30 P.M., drainage light yellow; 12.50 P.M., drainage light yellow. Duodenum now douched with 200 cc warm distilled water. At 1.05 P.M. bile drainage more freely, and slightly tinged with red; 1.20 P.M. drainage deep red; 1.30 drainage still red; 2.35 drainage, stain much lessened. Dog killed at 2.45.

Autopsy. Abdomen opened. Gall-bladder more flaccid, but not empty. Bile intermixed with dye. Stomach negative. First portion of duodenum negative; ampulla and 13 cm. beyond heavily stained.

Conclusion. Magnesium sulphate does not act as a specific hormone. Large amount of warm water obtained dye. Gall-bladder not empty.

In all of the foregoing experiments, great care was taken not to handle the gall-bladder, and no manual pressure was exerted on it.

Experiment V. Black male dog, weighing 52 pounds. Anesthetized with ether at 1.50 P.M. Carotids tied at 2.15 P.M. Decerebrated at 2.20 P.M. Dog in good condition at 3.15 P.M. Abdomen opened at 3.20 P.M. Duodenal tube introduced at 3.25 P.M., stitching duodenal tube in place. Gall-bladder moderately distended. Aspiration revealed small amount of blood-stained material. Five cc of stain injected into gall-bladder. Abdomen closed at 3.30 P.M.; aspiration reveals several cubic centimeters of grayish fluid, no bile being present; 3.35 P.M. 400 cc of warm magnesium sulphate (33 per cent) injected through duodenal tube. At 3.48 P.M., clear yellow fluid aspirated through duodenal tube; 3.55 P.M., clear yellow fluid; 4.10 P.M., clear yellow fluid; 4.20 P.M., restimulated with magnesium sulphate; 4.35 P.M., clear yellow fluid; 4.40 P.M., duodenum opened and small amount of bile-stained fluid present. No evidence of dye found. Dog now killed.

Autopsy. On opening abdomen, no apparent increase or decrease in size of gall-bladder found. No evidence of dye injected into gall-bladder in any part of intestinal tract. Stain still in gall-bladder. No obstruction present.

Conclusion. Apparently no increase or decrease in size of gall-bladder found. Free flow of bile; no change of pigments apparent. No evidence of dye found, showing duct sphincter may be relaxed and no gall-bladder elements present.

Experiment VI. White female dog. Dog anesthetized at 2.30 P.M. Carotids tied at 2.45 P.M. Decerebrated 3.00 P.M. Dog

in good condition at 3.15 P.M. Abdomen opened at 3.20 P.M. Gall-bladder moderately distended. Two cubic centimeters of stain injected into gall-bladder. Duodenum brought forward and anchored. Duodenum opened, but at no point could we find any evidence of bile, nor did any flow from the ampulla. At the end of ten minutes, 20 cc of warm magnesium sulphate was poured into region of ampulla. In ten minutes bile began to flow at irregular intervals of ten seconds, twenty-seven seconds, thirty-two seconds, and five seconds, keeping this irregular rate over a period of four minutes, at about four ejections per minute. Repeated applications of magnesium sulphate failed to cause any visual change in size of gall-bladder and no dye ejected.

Conclusion. No emptying of gall-bladder, nor presence of dye noted. Intermittent spurts of bile were visible, but no change of pigments occurred.

Experiment VII. Airedale, weight 40 pounds. Dog anesthetized at 10.45 A.M. Carotids tied at 11.20 A.M. Decerebrated at 11.30 A.M. Abdomen opened at 11.45 A.M., and duodenal tube stitched in place. This dog had been given no food for forty-eight hours, but was allowed water *ad lib.* Visual examination of the gall-bladder showed it to be more distended than that of any other dog. Dye injected into gall-bladder at 11.50 A.M. Duodenum now douched with 30 cc warm water. At 12.10 P.M. clear grayish fluid returned. No stain nor bile present. At 12.15 P.M., irrigated with 20 cc warm distilled water. This returned bile stained, but no dye was present. At 12.30 P.M. drainage still light yellow; 12.40 P.M. duodenum douched with 35 cc warm magnesium sulphate (33 per cent); 12.45 P.M. drainage still light yellow; 1.05 P.M., restimulated with magnesium sulphate; 1.20 P.M. drainage continued light yellow fluid; 1.30 P.M. duodenum irrigated through tube with 200 cc warm distilled water. Drainage continued light yellow color; 1.45 P.M. abdomen opened and duodenum opened. No evidence of dye was present. At 1.50 P.M., $\frac{1}{100}$ grain of eserin sulphate injected. No effect on gall-bladder noted. At 2.10 P.M., 1 per cent HCl washed over duodenum, which was followed by puckering of mucosa and ampulla.

Autopsy. Negative.

Conclusion. Fasting dog presented distended gall-bladder; no emptying of gall-bladder, and no dye ejected with use of eserin.

From the foregoing experiments, it seems possible at times to recover stain from gall-bladder injected with dye, and at times not. We did not use gravity as Graham did, and hence probably had more negative results. However, we believe that "B" bile is in part gall-bladder bile, because dye injected into the gall-bladder was recovered in three experiments, and where no dye was found, no change in pigments occurred. We also believe that at times gall-bladder bile may be obtained, and at times no gall-

bladder bile may be obtained with no apparent obstruction. Hence, care must be exercised before diagnosing obstructions of the cystic duct.

6. Is There a Chemical Change Which can Account for the Dark "B" Bile, or, in Other Words, an Oxidation of Pigments?

The chemistry of bile pigments is still in its infancy, and a great deal more work is needed before we will know all about oxidation and reduction of bile pigments.

Einhorn is of the opinion that the "B" fraction in a biliary drainage is a chemical change and bears no relationship to gall-bladder contents. He believes that it is the sulphate radical excreted by the liver which produces the darker bile.

Dunn and Connell claim it is the magnesium ion carried to the liver by the portal blood acting as a cholagogue producing a bile flow rich in pigment, or that it is the destruction of red cells by the magnesium ion somewhere in the portal system resulting in a sudden dumping of an increased quantity of blood pigment on the liver, which reacts by an increased output of bile rich in pigment. They also doubt "B" bile being gall-bladder bile on account of obtaining three types of bile in a case where the gall-bladder was out and the ducts destroyed.

Rous and McMaster, in experimental work on dogs, found that as long as the gall-bladder or any part of cystic duct was left, the bile remained pigmented, but if the gall-bladder and cystic duct were entirely removed, no pigmented bile remained, and the so-called white bile of surgeons was found.

In some later work, they found that in bile secreted against abnormally high pressure, as during partial obstruction, the pigment, cholate and cholesterol outputs are all cut down, and so much more is the fluid bulk that the concentration of substances per cubic centimeter of bile is notably lessened. They coin a new term "hydrohepatosis." They also believe in the existence of an enterohepatic circulation of pigment.

Chester M. Jones, in his work on bile pigments, found no relationship between the amount of magnesium sulphate given and bile pigments formed and also believes from his work that "B" bile is a mixture of gall-bladder bile and liver bile.

We do not believe that the sulphate radical or the magnesium ion bears any relationship to the dark pigment obtained in medical drainages. We also do not believe that the magnesium ion causes such a rapid destruction of red cells.

In test-tube experiments we have found that:

(*a*) Magnesium sulphate plus yellow ox bile : : No change in pigment.

(*b*) Alkali plus yellow ox bile : : No change in pigment.

(*c*) Alkali plus green ox bile : : Reduction in pigment.

(*d*) Acid plus yellow ox bile : : Change to green bile, oxidation of pigment.

(*e*) Acid plus green ox bile : : Change to dark green bile, oxidation of pigment.

(*f*) Yeast cells plus green ox bile : : Change in part to yellow bile, reduction of pigment.

(*g*) H_2S plus green ox bile : : Change to reddish bile, reduction of pigment.

(*h*) Air and light plus yellow ox bile : : Change to green bile, oxidation of pigment.

Gall-bladder bile is always darker than liver bile, which may be due to an oxydase being present in the gall-bladder, but this is not a proven fact. We do know however, that if the hydrogen-ion concentration of bile is shifted to the acid side, the resulting conditions are more favorable to oxidation of pigments.

According to McLeod, the pH of liver bile is 7.8, while the pH of gall-bladder bile is 5.3 to 7.4, that is, the H-ion concentration of bladder bile is higher than that of liver bile.

Dark or "B" bile may be obtained in medical drainages without any chemical agent being used, and the sphincter of Oddi may be relaxed by mere irritation of the metal tip, hence, this dark bile cannot be due to a chemical change and most likely is gall-bladder bile.

Warm distilled water will also bring forth spurts of dark bile and this also cannot be due to any chemical change.

Experiments VIII and IX. Two male dogs. Anesthetized with ether. The gall-bladder and bile ducts were exposed. A glass cannula was placed in the common duct, and 10 cc of a 25 per cent solution of magnesium sulphate was injected into portal vein. No change of pigments was noted in glass cannula over a period of forty-five minutes in either dog. If the magnesium ion could produce a destruction of red cells in the portal system it seems that magnesium sulphate injected directly into portal vein should also do so. However, in these two experiments no visible change of pigment could be noted.

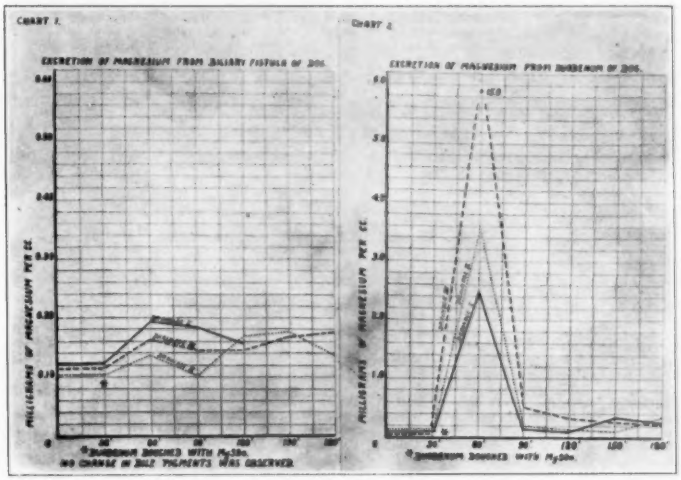
Various salts such as sodium sulphate, glucose, sodium bicarbonate, peptone, dilute hydrochloric acid, etc., all cause dark bile, hence it is hard to believe that they can all produce the same chemical change, or produce similar effects on pigments.

We have corroborated the findings of other men that magnesium can be absorbed and excreted by the liver. However, the excretion of magnesium bears no relationship to the type of pigment excreted. The large amounts of magnesium did not show the darker pigment. Hence, the sulphate radical or magnesium ion can bear no relationship to the dark pigment. This can be demonstrated by the following experiments, charts, and tables. The excretion of

magnesium was determined from a biliary fistula of a dog after instillations of magnesium sulphate into the duodenum.

The Drainages I, II and III shown by curves in Charts 1 and 2 and by figures in Table I, were done in the following experiments.

Experiment X. A medium sized white mongrel was anesthetized, a cholecystostomy and a Frank gastrostomy were performed. A small rubber tube was sutured in the gall-bladder and a duodenal tube was passed through the gastrostomy opening and anchored in the duodenum (linen suture used). The dog was given special care and progressed nicely.



Drainage I was on February 18, 1923; Drainage II was on February 19, 1923; Drainage III was on February 29, 1923. The drainage was done as follows: Drainage from the duodenal and gall-bladder tubes were collected separately in test tubes for a period of three hours, the tubes being changed every half hour. At the end of the first half hour 20 cc of a warm 33 per cent solution of magnesium sulphate were injected through the duodenal tube. This gave 12 specimens, 6 from the duodenum and 6 from the gall-bladder. The first 2 specimens were collected before the magnesium sulphate was injected, and were used as controls. The magnesium content of each specimen was determined by the method used by F. J. Tisdall and B. Kramer.[1]

[1] Jour. Biochem., 1921, **48**, 1.

TABLE I.—MAGNESIUM DETERMINATIONS.

Drainage I February 9, 1923 12.00–3.00 P.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	12.00–12.30	Brown	Alk.	1.10	1.0	0.1210	0.1210	0.1331
G. B. 2	12.30– 1.00	Brown	Alk.	1.35	1.0	0.1936	0.1936	0.2613
G. B. 3	1.00– 1.30	Brown	Alk.	1.25	1.0	0.1815	0.1815	0.2268
G. B. 4	1.30– 2.00	Brown	Alk.	1.20	1.0	0.1573	0.1573	0.1887
G. B. 5	2.00– 2.30	Brown	Alk.	0.40	1.0			
G. B. 6	2.30– 3.00	Brown	Alk.	0.30	1.0			
Duod. 1	. . . .	Yellow	Acid	18.0	1.0	0.1450	0.1450	2.6100
Duod. 2	. . . .	Yellow	Neut.	38.0	1.0	2.5710	2.5710	97.6980
Duod. 3	. . . .	Yellow	Neut.	13.0	1.0	0.1750	0.1750	2.2750
Duod. 4	. . . .	Yellow	Acid	21.0	1.0	0.1270	0.1270	2.6670
Duod. 5	. . . .	Yellow	Acid	16.0	1.0	0.2783	0.2783	4.4520
Duod. 6	. . . .	Yellow	Neut.	6.0	1.0	0.1210	0.1210	0.7260

20 cc of saturated $MgSO_4$ injected into duodenum at 12.30 P.M.

Drainage II February 10, 1923 1.45–4.45 P.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	1.45– 2.15	Brown	Alk.	3.6	1.0	0.1030	0.1030	0.3700
G. B. 2	2.15– 2.45	Brown	Alk.	1.6	1.0	0.1390	0.1390	0.2224
G. B. 3	2.45– 3.15	Brown	Alk.	1.3	1.0	0.1030	0.1030	0.1336
G. B. 4	3.15– 3.45	Brown	Alk.	1.0	1.0	0.1690	0.1690	0.1694
G. B. 5	3.45– 4.15	Brown	Alk.	1.3	1.0	0.1750	0.1750	0.2275
G. B. 6	4.15– 4.45	Brown	Alk.	1.5	1.0	0.1390	0.1390	0.2085
Duod. 1	. . . .	Yellow	Acid	24.0	1.0	0.1570	0.1570	3.7680
Duod. 2	. . . .	Yellow	Acid	41.0	1.0	3.5500	3.5500	145.5500
Duod. 3	. . . .	Yellow	Acid	6.0	1.0	0.1870	0.1870	1.1120
Duod. 4	. . . .	Yellow	Neut.	10.0	1.0	0.1270	0.1270	1.2700
Duod. 5	. . . .	Yellow	Acid	10.0	1.0	0.1090	0.1090	1.6900
Duod. 6	. . . .	Yellow	Neut.	7.0	1.0	0.2760	0.2760	1.9320

20 cc of saturated $MgSO_4$ injected into duodenum at 2.15 P.M.

Drainage III March 1, 1923 1.35–4.35 P.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt.,[a] mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	1.35– 2.05	Brown	Neut.	0.8	0.65	0.0785	0.1178	0.0970
G. B. 2	2.05– 2.35	Brown	Neut.	1.2	1.0	0.1633	0.1633	0.1959
G. B. 3	2.35– 3.05	Brown	Alk.	1.5	1.0	0.1452	0.1452	0.2178
G. B. 4	3.05– 3.35	Brown	Neut.	2.0	1.0	0.1452	0.1452	0.2904
B. G. 5	3.35– 4.05	Brown	Neut.	2.0	1.0	0.1694	0.1694	0.3388
G. B. 6	4.05– 4.35	Brown	Neut.	1.8	1.0	0.1754	0.1754	0.3157
Duod. 1	. . . .	Nellow	Neut.	1.0	1.0	0.0907	0.0907	0.0907
Duod. 2	. . . .	Yellow	Neut.	36.0	1.0	15.0700	15.0700	542.5000
Duod. 3	. . . .	Yellow	Neut.	16.0	1.0	0.5626	0.5626	9.0160
Duod. 4	. . . .	Yellow	Neut.	34.0	1.0	0.3267	0.3267	11.1070
Duod. 5	. . . .	Yellow	Neut.	22.0	1.0	0.2662	0.2662	5.8560
Duod. 6	. . . .	Yellow	Neut.	12.0	1.0	0.1210	0.1210	1.4520

20 cc of saturated $MgSO_4$ injected into duodenum at 2.05 P.M.

Drainages IV and V shown by curves in Charts 3 and 4, and by figures in Table II, were done in the following experiment:

Experiment XI. A large white bulldog was operated upon, and handled exactly the same as in Experiment X. The methods we used were the same as in Experiment X.

Drainages VI and VII shown by curves on Charts 5 and 6, and by figures in Table III, are estimations of magnesium from human biliary fistulæ. These were taken on two separate patients in whom a cholecystostomy was needed. The duodenal tube was passed in the usual manner, and 50 cc of a 33 per cent magnesium sulphate solution was injected into the duodenum and the magnesium was estimated in a similar manner to Experiments X and XI.

Chart 6 shows only one curve, namely that of Drainage VI.

The magnesium of the duodenal drainage in Drainage VII was not estimated because the amount of magnesium sulphate returned through a duodenal tube is variable and it was deemed unnecessary.

In 2 experiments on human biliary fistulæ it was noted that when the duodenum was douched with magnesium sulphate and

TABLE II.—MAGNESIUM DETERMINATIONS ON DOG BILE.

Drainage IV April 5, 1923 8.30–11.30 A.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	8.30– 9.00	Brown	Alk.	6.0	2.0	0.4054	0.2027	1.2162
G. B. 2	9.00– 9.30	Brown	Alk.	2.0	2.0	0.5204	0.2602	0.5204
G. B. 3	9.30–10.00	Brown	Alk.	6.0	2.0	0.4780	0.2390	1.4340
G. B. 4	10.00–10.30	Brown	Alk.	4.0	2.0	0.4780	0.2390	0.9560
G. B. 5	10.30–11.00	Brown	Alk.	3.0	2.0	0.4296	0.2148	0.6444
G. B. 6	11.00–11.30	Brown	Alk.	4.0	2.0	0.4054	0.2027	0.8108
Duod. 1	. . . .	Yellow	Neut.	1.0	2.0	0.3872	0.3872	0.3872
Duod. 2	. . . .	Yellow	Neut.	10.0	1.0	18.9800	18.9800	189.9800
Duod. 3	. . . .	Yellow	Neut.	1.0	1.0	1.3310	1.3310	1.3310
Duod. 4	. . . .	Yellow	Neut.	0.5	0.5	0.5990	1.1980	0.5990
Duod. 5	. . . .	Yellow	Neut.	1.0	1.0	0.7502	0.7502	1.1253
Duoe. 6	. . . .	Yellow	Neut.					

20 cc of saturated $MgSO_4$ injected into duodenum at 9.00 A.M.

Drainage V April 7, 1923 1.30–4.30 P.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	1.30– 2.00	Brown	Alk.	5.0	2.0	0.3384	0.1694	0.8470
G. B. 2	2.00– 2.30	Brown	Alk.	6.0	2.0	0.5142	0.2571	1.5426
G. B. 3	2.30– 3.00	Brown	Alk.	4.0	2.0	0.4478	0.2239	0.8956
G. B. 4	3.00– 3.30	Brown	Alk.	4.0	2.0	0.3750	0.1875	0.7500
G. B. 5	3.30– 4.00	Brown	Alk.	5.5	2.0	0.4052	0.2026	1.1165
G. B. 6	4.00– 4.30	Brown	Alk.	5.5	2.0	0.3024	0.1512	0.8316
Duod. 1	. . . .	Yellow	Neut.	2.0	1.0	0.3025	0.3025	0.6050
Duod. 2	. . . .	Yellow	Neut.	5.0	1.0	17.2550	17.2550	86.2750
Duod. 3	. . . .	Yellow	Neut.	1.5	0.7	2.5410	3.6300	5.4450
Duod. 4	. . . .	Yellow	Neut.	1.0	0.8	5.2032	0.6504	0.6504
Duod. 5	. . . .	Yellow	Acid	1.0	1.0	0.5022	0.5022	0.5022
Duod. 6	. . . .	Yellow	Neut.	1.0	0.9	3.6297	0.4033	0.4033

20 cc of saturated $MgSO_4$ injected into duodenum at 2.00 P.M.

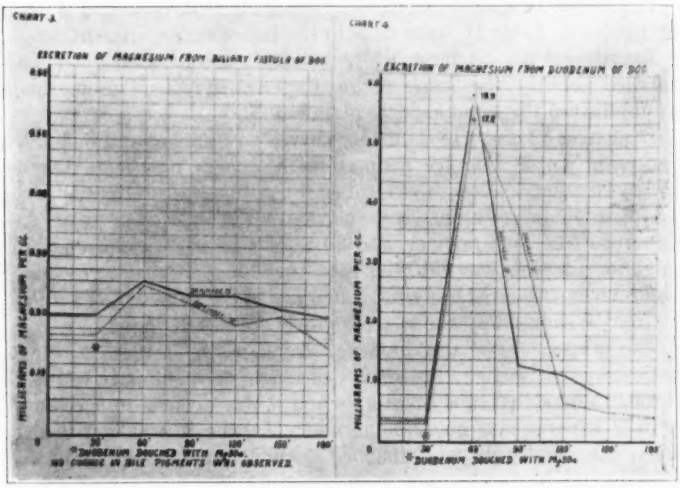


CHART 3.
EXCRETION OF MAGNESIUM FROM BILIARY FISTULA OF DOG
MILLIGRAMS OF MAGNESIUM PER CC.
* DUODENUM DOUCHED WITH MgSO4.
NO CHANGE IN BILE PIGMENTS WAS OBSERVED.
CHART 4.
EXCRETION OF MAGNESIUM FROM DUODENUM OF DOG
MILLIGRAMS OF MAGNESIUM PER CC.
* DUODENUM DOUCHED WITH MgSO4.

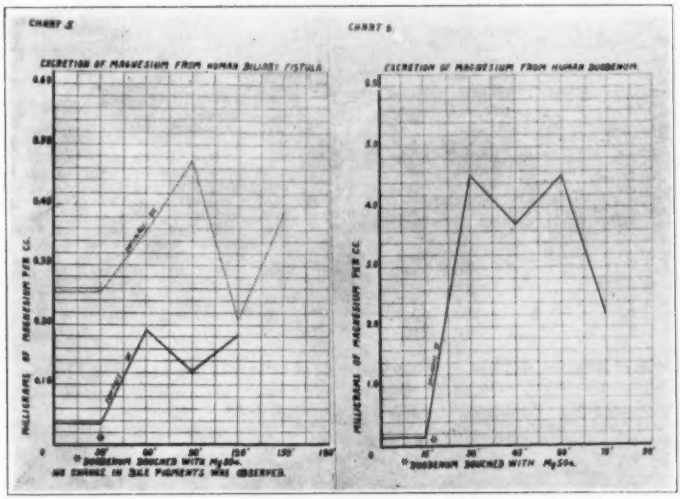


CHART 5.
EXCRETION OF MAGNESIUM FROM HUMAN BILIARY FISTULA
MILLIGRAMS OF MAGNESIUM PER CC.
* DUODENUM DOUCHED WITH MgSO4.
NO CHANGE IN BILE PIGMENTS WAS OBSERVED.
CHART 6.
EXCRETION OF MAGNESIUM FROM HUMAN DUODENUM
MILLIGRAMS OF MAGNESIUM PER CC.
* DUODENUM DOUCHED WITH MgSO4.

the bile drainage was free, the amount of biliary fistula bile decreased and then later again increased. This might be used as another point in favor of "B" bile coming from the gall-bladder. The figures are shown in Table III.

The bile pigments from the biliary fistulæ in dogs or in humans showed no change after douching the duodenum with magnesium sulphate, in periods over two hours. It might be noted that pigments coming from biliary fistulæ when freshly examined are lighter than bile pigments obtained from the gall-bladder at time of operation.

TABLE III.—MAGNESIUM DETERMINATIONS ON HUMAN BILE.

Drainage VI

	Time, min.	Color.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total, mag., mg.
G. B. 1*	30	Brown	9.0	5.0	0.1815	0.0363	0.3267
G. B. 2	30	Brown	3.0	2.5	0.4840	0.1936	0.5808
G. B. 3	30	Brown	2.0	2.0	0.2420	0.1210	0.2420
G. B. 4	30	Brown	2.0	2.0	0.3630	0.1815	0.3630
Duod. 1*	15	Yellow	20.0	5.0	0.8470	0.1694	3.3880
Duod. 2	15	Yellow	42.0	5.0	22.6270	4.5254	190.0668
Duod. 3	15	Yellow	39.0	5.0	18.6340	3.7268	145.3452
Duod. 4	15	Yellow	12.0	5.0	22.0220	4.5044	54.0528
Duod. 5	15	Yellow	52.0	5.0	10.8450	2.1690	112.7880

Drainage VII

	Time, min.	Color.	Volume, excreted cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total, mag., mg.
G. B. 1*	30	Brown	6.0	2.0	0.5082	0.2541	1.524
G. B. 2	30	Brown	3.5	2.0	0.7138	0.3569	1.249
G. B. 3	30	Brown	1.4	1.0	0.4719	0.4719	0.660
G. B. 4	30	Brown	4.0	2.0	0.4114	0.2057	0.822
G. B. 5	30	Brown	1.0	0.9	0.3484	0.3872	0.430

Drainage VIII

	Time, min.	Color.	Volume excreted, cc.
G. B. 1*	30	Brown	9.0
G. B. 2	30	Brown	1.0
G. B. 3	30	Brown	7.0
G. B. 4	30	Brown	5.0
Duod. 1*	15	Yellow	15.0
Duod. 2	15	Yellow	45.0
Duod. 3	15	Yellow	41.0
Duod. 4	15	Yellow	18.0

* Duodenum douched with $MgSO_4$.

COMPOSITION OF HUMAN BILE.
Parts per 100.

	Bladder bile.	Fistula bile.
Water	82.97	97.02
Solids	17.03	3.98
Bile salts	9.70	1.01
Mucin and pigment	4.19	0.48
Cholesterol	0.99	0.26
Fat	0.19	0.68
Soaps	1.12	0.26
Lecithin	0.22	0.64
Inorganic salts	0.51	0.92

We believe from the foregoing experiments that the magnesium ion or sulphate radical has no relationship to "B" bile.

Since our present knowledge of oxidation and reduction of bile pigments is still meagre, it seems to us most logical to assume that "B" bile or the dark pigment, comes from the gall-bladder. Oxidation and reduction undoubtedly are a variable factor and the future may throw more light on this most interesting problem.

7. IS ALL DARK COLORED BILE "B" BILE?

All dark bile is not "B" bile because we may get a slight change in pigments from dilated ducts, or stasis in the liver after the gall-bladder has been removed. This bile however, is not typical "B" bile, having less mucus and no gall-bladder elements, hence,

all dark bile is not "B" bile. The oxidation of pigments has been previously discussed, and need not be repeated at this time.

8. Does Magnesium Sulphate Have Specific Action, or Can Other Substances Likewise Cause Sphincter Relaxation?

This question has been answered with the other questions, earlier in the paper. Magnesium sulphate in our opinion, has no specific action, however, it relaxes the sphincter better than any reagent we have used. Magnesium sulphate, sodium sulphate, olive oil, dilute HCl, peptone, warm water, the duodenal tip, etc., may all cause sphincter relaxation.

McWhorter has demonstrated that a 25 per cent solution magnesium sulphate applied to the duodenum will reduce the resistance of the sphincter of Oddi, 50 to 100 mm. of water.

9. Is Medical Biliary Drainage of any Aid Diagnostically?

Most men agree that the examination of duodenal contents is of some value, hence biliary drainage must be of some value. Examination of any of the body secretions or excretions are of value, and this method affords the simplest way in which to recover bile for examination.

There is a great difference of opinion on the value of bile examination, yet the most radical must agree that if it tells nothing more, it will inform us as to the patency of the common duct. Gall-bladder diagnoses are often difficult, and any slight assistance may at times be of great value. It is impossible for the surgeon to lightly palpate or inspect a gall-bladder in an opened abdomen and say it is normal, for oftentimes on opening it, pathology is found, hence any method that will even slightly aid in diagnosis is of value. Early disturbances of liver function are also difficult to recognize, however, recently the work with phenoltetrachlorphthalein promises to be a great aid.

In our opinion, a good history is the most essential factor in making biliary diagnosis. The next in order is a careful physical examination, then the roentgen-ray and lastly the laboratory.

The profession is now justly reacting against using laboratory measures to the exclusion of good, common-sense, careful histories and physical examinations. There is no question that all methods at our disposal should be used and the laboratory at least should play a part in the routine of examinations, hence the examination of bile is also of value.

The examination of bile may be an aid, and yet it is not absolutely essential in all cases of biliary diagnosis. This however, is true of urine analysis, sputum analysis, and gastric analysis. If the duodenal contents are examined carefully before using magnesium sulphate and not many leukocytes are found, then after relaxation of the sphincter with magnesium sulphate many pus cells are found, we are justified in assuming biliary infection is present.

It is sometimes necessary to beware of being ultra-scientific and

trying to make hair splitting diagnosis for in most instances if checked up, the diagnosis is wrong. We feel that if it is possible to decide whether a gall-bladder is one for surgical or medical treatment, we have performed our duty.

Many men have apparently diagnosed obstructions of the cystic duct by this method, and oftentimes one can suspicion it after repeated stimulations with magnesium sulphate and no "B" bile being obtained. However, with our experimental and clinical observations to date, we feel that great caution should be exercised before attempting it, because there are many anomalies and pitfalls that may confuse us. If there is a definite obstruction of the cystic duct, the case is surgical, and we feel it better to diagnose our cases as such.

Cultures in our opinion are of definite value in some cases and we believe this fact can no longer be doubted. If cultures are carefully taken and proper attention is paid to the proper technic, it undoubtedly is an aid in location of focal infection. If two or three duodenal cultures are negative, and then after magnesium sulphate stimulation a relaxation of the sphincter of Oddi occurs and a bile culture is taken and proves a positive streptococcus on two or more cultures, then we are justified in placing the infection in the biliary tract.

If after a cholecystectomy the patient is not cured, and a positive culture is obtained, it immediately informs us that the ducts are still infected.

By cultural methods in biliary drainage, typhoid carriers may be detected, and hence it is of decided value.

The significance of cholesterin crystals is another interesting problem. The gall-bladder undoubtedly contains more cholesterin than any other organ of its size, and finding an increased cholesterol content of "B" bile is another point in favor of "B" bile being gall-bladder bile. The relationship of the cholesterin of the blood and the cholesterin content of the gall-bladder is still a disputed point. An increased cholesterol content in the blood with gall-bladder symptoms is regarded by some to be in favor of cholelithiasis. However, others doubt the value of this laboratory finding.

It is true that many gall-stones are cholesterin stones, but whether or not cholesterin crystals of themselves denote gall-stones, is a purely hypothetical assumption. One may find many cholesterin crystals in a biliary drainage, and yet at operation no stones are found. However, if many crystals are found, and the other symptoms coincide, it may sway the balance in favor of stones.

We feel that macroscopical blood and little or no bile on stimulation with magnesium sulphate in connection with other physical signs aids us in the diagnosis of malignancy of the ampulla of Vater.

Palefski has used the duodenal tube as a method of visualization

of the duodenum, and thinks a distorted curve denotes evidence of periduodenal adhesions.

Biliary drainage aids in the diagnosis of certain types of headaches. This method affords great relief in biliary headaches, and hence is an aid in their diagnosis.

To summarize, it is our opinion that the diagnostic values of biliary drainage, are as follows:

(*a*) It gives definite information as to the patency of the ducts.

(*b*) It aids in diagnosis in some cases of malignancy, especially of the ampulla of Vater.

(*c*) Real dark thick bile denotes biliary stasis.

(*d*) Positive cultures denote biliary infection, and are another means of locating foci of infection.

(*e*) It aids in locating some typhoid carriers.

(*f*) In postoperative cases, with return of symptoms, it determines the patency of the ducts, and whether or not infection is still present.

(*g*) Gall-bladder sand may aid in the diagnosis of stones. However, we have not observed this as often as reported by others and consider it of little value.

(*h*) It aids in the diagnosis of pancreatitis.

(*i*) It is of value in duodenal visualization.

(*j*) It assists in differential diagnosis of right upper quadrant lesions.

(*k*) It aids in the diagnosis of certain types of headaches.

10. Is Medical Biliary Drainage of Any Value as a Therapeutic Procedure?

Biliary drainage, as a therapeutic agent, has its limitations, but if used rationally, it is undoubtedly of great benefit in many cases.

Surgery is still the preferable means of attack in most biliary lesions, and will continue so, because infections of the gall-bladder are mostly submucosal and in the wall, hence medical drainage will not relieve the infection as well as surgery.

Medical biliary drainage offers some cures in biliary lesions, however, it is more of a palliative procedure than curative.

Some men claim that its value is purely psychic, and no real pathology can be relieved. It has undoubtedly a great psychic factor, but this alone cannot explain the real benefits obtained by all cases. It will be impossible in this paper to cite a long list of cases, but the literature is so full of beneficial results reported by good men, that there can be no question that it has some value.

We often forget that our patients come for relief of their suffering, and if medical drainage relieves them, whether it be psychic or otherwise, our beneficial result is obtained.

We believe medical biliary drainage is indicated in the following cases:

(*a*) In cholecystectomized patients with return of symptoms.

(*b*) In catarrhal jaundice.

(*c*) In biliary headaches.

(*d*) In cases where surgery is contraindicated: (1) old people; (2) heart cases; (3) diabetics.

(*e*) It aids in clearing up typhoid carriers.

(*f*) It is of value in pre- and postoperative treatment of biliary infection.

(*g*) It benefits so-called biliousness and lethargy.

(*h*) It aids in treatment of pancreatitis.

(*i*) It benefits enteroptoticers with pain in the upper right quadrant. (This may be psychic.)

(*j*) It assists in preventing postoperative vomiting.

11. In What Manner is Biliary Drainage of Value and Would Gastric Lavage Afford as Much Relief as Biliary Drainage?

We feel that biliary drainage assists in ridding the body of toxic material because duodenal lavage is of value in any toxic condition and has been recommended in toxemias of pregnancy.

It is an excellent aid because it increases the flow of bile. By increasing the flow of bile it must assist Nature in ridding itself of infection as well as of toxemia.

It indirectly flushes the liver, if one may use this crude expression, by drawing off more fluid from the liver, hence more fluid must of necessity be attracted toward the liver.

It acts as a temporary drain to the biliary passages and liver similar to a surgical drainage, hence assists in relieving infection.

By its catharsis it also rids the colon of stasis.

It is of great psychic value. The psychic side of a patient is frequently overlooked by many medical men, therefore oftentimes failures are present when success could be obtained.

Some claim that magnesium sulphate by mouth is just as efficacious as biliary drainage, however, anyone using biliary drainage in an unprejudiced manner over a long period of time, knows that it is lack of experience that prompts this statement.

Let us not condemn any method of procedure until you have given it a fair and unprejudiced trial. Likewise, do not recommend a simple procedure as a cure-all for any condition. Weigh each side carefully and then let experience be your guide.

We do not feel hyperenthusiastic about medical biliary drainage, for it has its limitations, yet if used conservatively and properly it undoubtedly is of value.

Summary. The gall-bladder does contract, however, its contraction power is minimal. The gall-bladder and the common duct sphincter are probably regulated by a definite reflex mechanism; however, more proof is needed before it is an accepted fact. Gall-bladder contraction alone does not empty the gall-bladder and

other external factors assist in expelling part of its contents. "B" bile is in part gall-bladder bile. The gall-bladder is more than a mere reservoir and undoubtedly has definite function even though these functions are not essential to life. The chemistry of bile pigments is still in its infancy. However, the action of the magnesium ion or the sulphate radical on the liver does not explain the dark bile, and likewise the magnesium ion does not cause a large destruction of red cells in the portal system producing a dark colored bile more rich in pigments. Slight changes in bile pigments may occur in cholecystectomized patients. Magnesium sulphate does not act like a hormone for other substances have like action. Biliary drainage is of some value diagnostically, but in a more limited way than expressed by some writers. In our opinion it is of no value in differentiating cholecystitis from cholelithiasis. It is an aid in locating infection in some cases of biliary disease. It is also a well known fact that gall-bladder bile is often sterile and hence a positive culture will not definitely localize, which part of the biliary tract is involved. It is of more value in determining if infection is still present in cholecystectomized patients. Biliary drainage is of more value as a therapeutic adjunct than as a diagnostic agent. It is curative in mild cases; however, it is to be used more as a palliative measure than a curative agent. Surgery is our best means of attack in most biliary infections. Biliary drainage has definite therapeutic value other than being a mere psychic aid.*

THE KOLMER MODIFICATION OF THE COMPLEMENT-FIXATION TEST FOR SYPHILIS: ITS RELATION TO THE CLINICIAN AND TO THE REQUIREMENTS FOR A STANDARD TECHNIC.†

By Robert A. Kilduffe, A.B., A.M., M.D.,
Los Angeles, Calif.

(From the Laboratories of the Pittsburgh Hospital.)

A great deal of water has passed under the bridge since Wassermann, in 1906, described the complement-fixation test for syphilis commonly known by his name, although, strictly speaking, the name is practically the sole remaining vestige of the method originally described.

* The references, ninety-one in number, are omitted from this article on account of lack of space but will be found in the author's reprints.

† Read before the Second Annual Convention of the American Society of Clinical Pathologists, San Francisco, June 26, 1923.

Probably no other single laboratory test has been subjected to more extensive and intensive investigation than this procedure, and while the preponderance of the literature was, in the beginning, largely the result of studies in laboratory technic and the product of the serologist, present studies are more properly the combined or, at least, the correlated production of serologist and clinician working in unison. This, beyond cavil, is as it should be, for while studies leading to refinements and perfection of technic are of value, their value is in direct proportion to, and directly determined by, the acid test of clinical interpretation and evaluation. Neither by serologist nor by the clinician working alone can the ultimate dictum be laid down; only as a result of the close and sustained coöperation of both can the final word be said as to the relative merits of this or that method of technic.

It is essential, therefore, that in the evaluation of any new method for performing this test, and particularly when the method is proposed as a standard technic for general adoption, that the study be not confined solely to the laboratory but conducted with the close coöperation of the clinician upon whose shoulders the responsibility for the interpretation of the reaction finally falls. This is especially necessary because syphilis, on account of its prevalence and the protean character of its manifestations, is a condition the recognition and handling of which is, in the main, not relegated to those especially trained or particularly interested and adept, but is rather a condition continually confronting the man in general practice; and it is upon his recognition of the infection that the ultimate success or failure of treatment in no small measure depends.

Any method to succeed as a claimant for general adoption, in the study of this disease, therefore, must be judged not alone by its feasibility in the laboratory; not alone by its value when interpreted by the specially trained expert; but in terms of its value to the practitioner in general; for, rightly or wrongly, momentous decisions will, at times, hang upon the result of an isolated serological examination. It is not the purpose of this communication to discuss the inadvisability of such an undue reliance upon the results of a single test; that has been done elsewhere[1] [2] and by many writers. It is purposed, rather, to consider the requirements to be fulfilled by a standard technic with particular reference to those formulated by the clinician.

To this end a series of slightly over 2000 tests will be considered from these standpoints, but, just as it is impossible to study satisfactorily the complement-fixation reaction from the laboratory standpoint alone, so it will be impossible to study this series from the clinical angle alone, for both are interrelated and both will be deciding factors of importance in determining the adoption of a standard technic.

The sera comprised in this series include those subjected to

routine examination in a variety of conditions in the medical, surgical, gynecological, and obstetrical wards of the Pittsburgh Hospital; sera sent in for diagnosis; sera from known syphilitics under treatment; and sera from "Morals Court" cases secured by Dr. A. H. Eggers, County Medical Inspector, Pennsylvania State Department of Health, and comprising a large number of prostitutes and persons of ill repute, many of whom were syphilitics under treatment. In addition to these, 104 cases of tuberculosis in all stages were subjected to a Wassermann test by the Kolmer modification, these last being secured through the courtesy of Dr. Joseph Shilene. To these gentlemen, and particularly to the Chiefs of Staff of the Pittsburgh Hospital, sincere acknowledgment is due for their unfailing coöperation. All sera were tested in exact accordance with the technic as described by Kolmer.[3,4]

Analysis of the Series in Relation to the Requirements for a Standard Technic. I. SIMPLICITY OF TECHNIC.—As pointed out by Kolmer,[5] and as is obvious, simplicity must be looked upon as a relative term when used in connection with complement-fixation reactions. Any method will present complexities to the inexperienced and inadequately trained worker—who should not be permitted to conduct even the simplest such test if it is to be done merely by "rule of thumb"—whereas, to the experienced serologist, or even to one not overburdened with experience but whose preparatory foundation has been well grounded, the Kolmer modification will present no manipulative difficulty. It will require care and attention, as will any method, while skill and rapidity in its execution are a matter of practice and grow with experience.

From the standpoint of its feasibility in a technical sense the conclusions drawn from practical experience with the method are entirely favorable and the test conforms to this requirement for a standard method. This conclusion is further confirmed by the fact that in none of the reports so far made concerning this method has any criticism been made of it from the standpoint of manipulative difficulty.

II. ECONOMY OF MATERIALS.—This is a matter of importance, not only in laboratories performing large numbers of tests, but also in those utilizing the method in a relatively small number. It is met in the Kolmer modification by the use of preserved complement which, preserved either by the use of sodium chloride (0.3 gm. to 1 cc of serum), or of sodium acetate, (1.5 parts of 12 per cent aqueous solution to 1 part of complement serum), will retain its activity for at least four weeks.

It is important to bear in mind, however, that the *fixability* of complement begins to show deterioration before its hemolytic activity is impaired and that, therefore, it is imperative that a known positive control be always included in the set-up. As an added precaution, it is my practice never to use a complement when more

than two weeks old; in an active laboratory, the serum will generally be used up before the expiration of this time.

While the initial expense of preparing the new antigen used in conjunction with the test[6] is probably increased over that of ordinary methods, the resulting extract is so stable and so extraordinarily antigenic, thus permitting its use in small quantities and over long periods of time, that, in the end, it is probably cheaper than the continued maintenance of a supply of various extracts. As a maximum of 0.3 cc of serum and 1.5 cc of spinal fluid—quantities easily obtained—are sufficient for the performance of the quantitative reaction, from the standpoint of economy in materials, therefore, the method also qualifies as a standard technic.

III. Economy of Time.—Here, having a primary incubation period of twelve to eighteen hours (thus requiring two days before a report can be made) the method presents a distinct variance from accustomed procedure.

It becomes necessary, therefore, to inquire, first, if the rendering of reports within a few hours is an essential feature of a standard technic from the standpoint of either serologist or clinician, and, second, if such rapid reporting is an actuality in practice?

As to the serologist, the increased time is a matter of little moment. The addition of the hemolytic system and the secondary incubation is a small thing on the second day and the added confidence in the results obtained and the general satisfaction given by the method in practice more than compensate for the added time required by the extended primary incubation. Whether or not this long primary period is a *sine qua non* of the method the consensus of experience will determine in time.

Now as to the clinician: Man is a creature of habit and clinicians are no exception to this rule. The habit of many years has accustomed him to the receipt of reports and the completion of the test within a matter of hours and any change from this procedure will, undoubtedly, at first give rise to discussion and even, perhaps, to protest.

It behooves us, therefore, to consider, first, whether or not it is essential for reports to be made within a few hours; and, second, whether in practice this is commonly the case?

In the first place, when considering if it is essential, necessary, or desirable that reports be rendered within a few hours or on the same day that the blood is taken, it is necessary to ascertain the reason for this precipitate haste. It cannot be because of any added danger to the patient by reason of the spread of the infection beyond controllable limits, for if syphilis is to be averted the preventive measures must be initiated within at the most two hours after exposure when neither lesion nor Wassermann reaction are present and, moreover, the treatment of syphilis can never be limited to any definite time regardless of when it is initiated. It cannot be

because the delay, even of days, is unwarrantedly dangerous in the known or suspected syphilitic, for the treatment of the disease is a tedious affair at best and, as a matter of fact, for various reasons, many cases do not report to the doctor again for several days after the blood has been taken, or do not come "until next dispensary or clinic day"—which may be several days off—and, in many others, treatment will not be begun for an appreciable time after the report has been made. Even were the delay deleterious, therefore, as a matter of fact it occurs quite frequently nevertheless. Syphilis is not a disease in which life, death, or ultimate cure is a matter of hours or even days; efficient treatment is a matter of years and while it is true that the earlier treatment is begun, the better the ultimate expectations, a delay of even several days is a matter of little moment in the last analysis. In the early case by the time a positive complement-fixation reaction has appeared the disease has spread beyond local limits; in the late case or one discovered years after insufficient treatment a further delay of a few days before again starting treatment is of little importance.

Secondly, is this matter of rapidity in making and reporting the Wassermann test a fact or merely a fictitious actuality? In this connection the following facts are of interest:

(*a*) In many laboratories, especially in hospitals, the Wassermann test is made only upon certain days and several days may elapse between the taking of a specimen and the rendering of a report; in fact this is a frequent occurrence and under these circumstances no protest is made by the clinician because these circumstances are a matter of habit and custom.

(*b*) Many specimens are sent to laboratories by mail and thus varying periods of time are consumed in transit and the examination therefore, delayed. This, again, is a matter to which the clinician is accustomed and so causes no discussion.

(*c*) At times bloods are held for appreciable periods of time before transmission to the laboratory and, if properly kept, no harm seems to be done by the delay thus occasioned in making the report.

(*d*) Many patients directed to report to the serologist for the taking of a specimen take their own time for so doing, thus adding days and sometimes weeks to the period elasping between the requisition, so to speak, and the making of the test.

On analysis, therefore, the matter of a few days more or less between the collection of the specimen and the rendering of a report does not seem to merit the importance given to it at first glance and so does not act as a formidable obstacle in the adoption of a standard technic. In this respect, therefore, the Kolmer modification as described, if it does not actually qualify as a standard method, cannot be said to be disqualified by reason of the extra day required. It is simply a matter of becoming accustomed to the added day.

IV. SPECIFICITY.—This is a very essential requirement of any method and particularly so for a standard technic. It demands: (*a*) That the reaction, when positive, shall indicate the presence of syphilitic reagin; and (*b*) that positive reactions shall not occur in the absence of the disease.

The Significance of Positive Reactions with the Kolmer Method. As is well known, the Wassermann test is not a biologically specific reaction and, hence, only relative specificity can be expected and in the past, though non-specific reactions with carefully controlled technics were relatively rare, still they occurred. To the clinician this is a matter of great moment for the making of a false diagnosis based upon a non-specific fixation may be fraught with dire consequences to all concerned.

Certain conditions are well known to give non-specific fixation with syphilitic antigens when tested by methods in ordinary use and it is of interest, therefore, to consider what are the results obtained in them with the Kolmer modification.

1. *Yaws.*—No report has been found in the literature at hand concerning the use of Kolmer's modification in this disease and the condition is not among those included in the present series. It is probable, however, that on account of the similarity between the *Spirocheta pertenuis* and the *Spirocheta pallidum*, the reaction by this or any other method, would be positive. The clinical differentiation of the two diseases, however, does not make this a cause of confusion.

2. *Pneumonia during the Febrile Period.*—In this series there were 8 cases of pneumonia in which the blood was tested during the febrile stage. In 7 of these the Kolmer modification gave a clear-cut negative, one serum giving a 44410 reaction. This case was again tested during convalescence, again gave a positive reaction and a history of infection three years previously was obtained. While this number of cases is too small to warrant any far-reaching conclusions, the results are significant and of some importance and warrant a further study of the blood in pneumonia.

3. *Blood from the Umbilical Cord.*—While notoriously unreliable, these specimens are, nevertheless, frequently taken and often constitute the sole available avenue of investigation, as has been noted elsewhere.[7] In this series a total of 85 cord bloods were subjected to examination, 81 of which gave negative reactions, there being 4 positives: 44300, 33100, 02210 and 04310. In 3 of these cases a specific history was obtained, infection being denied in the fourth and direct examination of the mother and father being refused. Here, again, the number of specimens examined was too small to permit of final conclusions, but the absence of non-specific fixations and the corroboration of the positives obtained is a remarkable tribute to the specificity of the reactions obtained with this technic.

4. *Leprosy.*—No personal experience has been had with this infection, efforts to obtain leper sera having failed. Kolmer states,[8]

however, that the method has given consistently negative results in a relatively large number of leper sera.

5. *Tuberculosis.*—This is one of the conditions which, at various times, has been said to cause non-specific cross-fixation with syphilitic antigens. The consensus of observation, however, tends to show that this is not the case when a carefully controlled technic is used and the occurrence of a positive syphilitic complement-fixation in a tuberculous serum, therefore, necessitates a careful examination for evidences of syphilis which, however, may not be found clinically and be demonstrable only at autopsy.

In the present series there were 104 cases of tuberculosis in various stages. Of these 10 gave positive reactions with the Kolmer modification. In 2 of these cases a specific history was obtained, one having had a chancre thirty-five years before and giving a 11100 reaction, the other giving a 44440 reaction and admitting a chancre eight years before. A third with a 44444 reaction presented a typical secondary rash clearing up under antiluetic medication; fourth, while denying any history, presented a general adenopathy, and admitted irregular habits. In 4 cases no history was obtained and no definite clinical evidence of syphilis was found, while the remaining 2 cases were lost.

Here, again, the series permits only of generalizations. In view however, of the results obtained with the series as a whole and, also, of the conclusions formulated by other workers with the Wassermann test in tuberculosis, it is quite likely that all of the reactions obtained represented the presence of syphilitic reagin.

Included in the series there were, of course, a large number of varied, non-syphilitic conditions not necessary to tabulate. Of extreme interest and practical value, however, are the facts that, first in no instance where non-specific fixation commonly occurs did fixation occur with the Kolmer modification; and, second, in no instance where fixation occurred and where historical or clinical data were obtainable did these fail to corroborate the results of the test.

It would appear, therefore, that non-specific, false positive reactions are encountered only with extreme rarity with this method, if, indeed, they occur at all.

The combined reports which have so far been published and to which I have had access give a total of 8877 reactions by Kolmer's modification as follows:

Observer.	Number of tests.
Kilduffe[9] (previous report, 1014; this report, 1000)	2014
Schamberg and Greenbaum[10]	4000
Shivers[11]	320
Harper and Curtis[12]	120
Palmer and Gibb[13]	329
Smith[14]	94
Schamberg and Klauder[15]	2000
	8877

In none of these cases were false positives encountered, a fact specially noted by all of these observers. It is safe to say that no other technic in like series and comprising a like variety of conditions has ever given similar results and the results of the combined series tend to indicate that with the Kolmer test non-specific positive reactions do not occur.*

If the cumulative results of other workers substantiate this apparent claim then the method at once establishes a predominant and almost unassailable place in the serological diagnosis of syphilis. To prove or disprove this possibility becomes the duty of all serologists and clinicians interested in syphilis.

In the face of these results the added time necessary to perform the test becomes a matter of extreme insignificance.

Results in Syphilis with Kolmer's Modification. The conclusions drawn from an analysis of the series previously reported[16] are substantiated by the additional experience upon which this report is based and can again be emphasized:

1. A positive reaction obtained with Kolmer's method may be looked upon with a high degree of reliance as indicative of the presence of syphilitic reagin in the blood.

2. A false positive reaction in the absence of syphilitic reagin was not encountered in this series of 2000 cases nor in 8877 cases reported by other observers and is, therefore, an extreme rarity, if, indeed, it occurs at all.

3. The method will detect extremely minute quantities of reagin and, moreover, quantitatively expresses the amount detected.

V. DELICACY. This quality is of vital importance as weighing for or against the adoption of a standard technic for the reasons following:

1. The clinical diagnosis of syphilis is not always an easy nor a simple matter, regardless of the skill of the observer. A standard test, therefore, should be able to detect the disease when clinical signs fail and should be most reliable where skill in diagnosis is at a minimum.

2. The test should be able to detect reagin as early in the infection as possible.

3. Not only gross but minute quantities of reagin should be demonstrable.

4. The reaction should be suitable for the estimation of the efficiency of treatment.

5. False negative reactions should not be obtained with undue frequency.

6. While the occurrence of anticomplementary substances in the serum tested is often due to circumstances beyond the control of the

* At the meeting before which this paper was presented, a number of reports were made by various workers bringing the total number of reactions of Kolmer's technic without demonstrable false positive reactions up to a little over 30,000.

laboratory and the serologist and, at times, of the clinician, such reactions should occur with a minimum of frequency.

In the consideration of the question of delicacy as regards the diagnostic detection of reagin it is, of course, necessary to bear in mind that a certain time must elapse after the appearance of the chancre before reagin appears in the blood in detectable amounts. This time is generally placed at a minimum of twenty-one days—and safely so—and in this connection it is interesting to note that in this series reactions have been obtained as early as three (10,000), four, five, seven, and ten days after the appearance of the initial lesion. While such an early detection of reagin is not to be looked for routinely nor to be diagnostically relied upon, it is a significant tribute to the delicacy of the technic.

The most important conditions formulated by the clinician to be fulfilled by a standard method are that it shall detect reagin with a high degree of accuracy and delicacy and that it will serve as a reliable and efficient control of treatment. The first condition has, to all intents and purposes, been covered in the preceding paragraphs in the consideration of the specificity of the reactions obtained with Kolmer's method. It must be noted here, however, that while a positive reaction can be taken, in view of the evidence at hand, as almost absolute evidence of the presence of reagin in the blood, a like condition does not obtain in the interpretation of the significance of an isolated negative reaction.

In the 2000 cases examined, negative reactions occurred in 14 or 0.7 per cent, in all of which syphilis was undeniably present, some being cases under treatment and giving a positive fixation by another technic.

The occurrence of such false negatives is common to all complement-fixation methods and is illustrative of the vital necessity for repeated serological examinations, not only in the control of treatment, but especially when the test is used as a means of diagnosis. It is essential to remember that the presence of syphilitic reagin is an expression of the interaction of the spirochetæ and the body tissues and its absence at a given time, unless corrobrated by repeated observations, is simply an indication of the absence of interreaction between the organisms and the tissues with consequent non-production of reagin or of its production in detectable amounts.

Many authorities have called attention to the fact that syphilitic reagin is not produced in mathematical proportion to the severity of the disease, that it may present a wide range of reactions in known syphilitics without demonstrable cause, and many serologists have noted its selective preference for various antigens.

At the risk of repeating observations made elsewhere[17] as well as the observations of others, it is well again to emphasize the fallacy of relying upon a single negative complement-fixation reaction as conclusive evidence of the absence of syphilitic reagin or

infection. A single negative Wassermann test by any method as yet devised can never be allowed to overshadow the presence of clinical evidences of lues nor can it be made the sole criterion of a sufficiency of treatment. The method may be standardized as to technic but there will always be an unknown quantity impossible to control—the patient. He may be syphilitic and yet, at times, show a marked fluctuation of reagin without demonstrable cause; or it may even be absent, or again, if present, it may fix well with one antigen while reacting indefinitely with another. It would seem trite to emphasize the dubious value of a single negative reaction were it not for the fact that in a surprising number of cases a single Wassermann test is made to take the place of a careful history or even, at times, of anything more than a perfunctory physical examination.

The clinician, therefore, can never place the same degree of reliance in a single negative reaction as can be placed in a positive reaction with Kolmer's method, even though it may be noted that false negative reactions appear to occur with this technic in a minimum of cases.

The Kolmer Method as a Control of Treatment.—It is in the examination of treated cases that this method displays a particular efficiency. A significant feature of the reaction is that it remains positive perceptibly longer than other methods and so leads to more prolonged and, therefore, more efficient treatment before negative reactions can be obtained.

The graphic character of the strictly quantitative readings is of the greatest value as forming a definite index to the degree to which it should be pursued. Of no less importance, as will be noted in a subsequent communication,[18] the readings may be graphically utilized to present to the patient the serological effects of treatment and so encourage him in the persistence necessary to effect a cure; while, for the same reasons, the method is particularly adapted to the study of the efficiency of various therapeutic agents. All observers reporting on the method are unanimous in extolling its efficiency as a control of treatment and none more emphatically than the clinicians.

The occurrence of positive reactions early in the infection is a feature of great practical importance because, as has been noted by Schamberg and Greenbaum,[18] a definite number of primary lesions are negative to dark-field examination as a result of local treatment; and generally negative serologically because the time of the appearance of the reagin in the blood varies with the individual and the sensitiveness of the test employed. The fact that Kolmer's method will not only detect the presence of reagin—but also measure the amount—in as little as 0.0025 cc of serum is a sufficient testimony to its delicacy.

VI. A STANDARD METHOD MUST BE A QUANTITATIVE METHOD.—This has ceased to be a debatable requirement and is conceded by both the clinician and the serologist. Kolmer's method is not only a strictly quantitative method in that it measures the least amount of serum containing reagin, but it also permits of a further refinement in indicating, in terms of +4 to +1 the amount of reagin present in each serum dilution, thus permitting a distinction between a 44444 and 44321 reaction, although both are "very strongly positive."

VII. DEFINITE READINGS SHOULD BE POSSIBLE IN A HIGH PERCENTAGE OF CASES.—Because of the, at times, unavoidable factors operating to make a serum anticomplementary, such readings will always occur in a varying proportion of cases. With Kolmer's method, however, these are reduced to a minimum, occurring only in 4 cases or 0.2 per cent of 2000 sera in spite of the fact that many were such as would have been—and were—anticomplementary with other methods.

VIII. AGREEMENT WITH CLINICAL FINDINGS.—For the clinician this is almost a *sine qua non* of a standard method. All observers working with Kolmer's method are unanimous in emphasizing the agreement with the clinical findings in a high percentage of cases, an experience borne out in the series herewith reported, so that this requirement is more than fulfilled and in this respect the method qualifies as a standard technic.

Summary.—An analysis is presented of the Kolmer modification of the complement-fixation test in syphilis in a series of 2000 sera in relation to the requirements of the clinician and to those suitable for a standard method. As a result of the data presented, it is concluded that the method is suitable for adoption as a standard test and superior to any as yet proposed for the purpose.

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THE USE OF INSULIN IN THE MODERN TREATMENT OF DIABETES.*

By David S. Hachen, B.S., M.D.,

Instructor in Medicine, University of Cincinnati; Resident Physician, Cincinnati General Hospital.

(From the Medical Clinic, Cincinnati General Hospital, University of Cincinnati.)

Insulin is the internal secretion of the pancreas. It is the substance which is supplied in insufficient quantities in diabetic individuals. Ever since Langerhans demonstrated the islet tissue in the pancreas and Opie established the hypothesis that diabetes was due to degeneration of this tissue, many investigators have made innumerable, but unsuccessful attempts to extract this substance.

Banting and Best[1] prepared the substance now known as insulin from dog's pancreas removed from seven to ten weeks after ligation of the ducts. Later[2] they prepared it from the pancreas of the bovine fetus at about the fifth month. Then Collip,[3] by means of an elaborate process, prepared insulin used in the first clinical cases, from the whole gland of the adult ox. Extracts prepared by these procedures when injected intravenously and subcutaneously in diabetic animals reduced the percentage of the blood sugar and the daily urinary excretion of sugar. Likewise the blood sugar of normal rabbits could be markedly reduced but when 0.04 per cent was reached convulsions occurred. This finding was made use of in establishing insulin dosage. Thus the term "unit of insulin" was given to that amount which would lower the blood sugar of a starved rabbit to 0.04 per cent, that is, the convulsion point, in from one to four hours. After these facts and others were established, insulin was used on human diabetics with similar results. Banting, Campbell and Fletcher[4] have recently reported a series of over 50 cases treated

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with insulin attended with marked clinical improvement, abolition of the glycosuria, maintenance of the blood sugar at the normal level and disappearance of ketones from the urine and blood.

Regardless of the marvelous effect produced by the administration of insulin in human diabetics, great stress must be laid on the dietetic management. Diet still maintains its paramount position in the treatment of diabetes and will therefore be given the first consideration.

In the management of a successful diabetic diet the following points must be considered; (1) the carbohydrate content, (2) the protein content, (3) the fat content and (4) the total caloric content.

The Carbohydrate Content. The efficacy of keeping the carbohydrate content of the diet below the glucose tolerance of the patient is generally conceded. Woodyatt[5] regards sugar as a stimulant to the sugar-burning mechanism. Thus, the presence of excess of sugar in the metabolic mixture stimulates a diseased pancreas to the point of fatigue and lessened function. Theoretically, then, diminution in the glucose supply should relieve this organ and give it a chance to recuperate. Carbohydrate reduction is always attended with clinical improvement. It seems justified on these grounds, therefore, to keep the carbohydrate content of the diet at a minimum, compatible with the prevention of ketosis.

The Protein Content. A minimum of protein, just sufficient to maintain nitrogen equilibrium, should be used for four reasons: (1) because ingestion of protein throws a large amount of glucose (58 per cent by weight) into the metabolic stream; (2) because the relatively high specific dynamic action of protein produces an undesirable elevation of the basal metabolic rate, as demonstrated by Wilder, Boothby and Beeler;[6] (3) because the work of Wilder[7] shows that an excess of protein exerts a specifically depressant effect on the ability of the organism to utilize glucose; and (4) because protein per gram of substance is not as effective in the prevention of ketosis as carbohydrate per gram of substance.

Marsh, Newburgh and Holly[8] recently published a review of the literature bearing on the minimal protein requirement and concluded that in the diabetic as in the normal, $\frac{2}{3}$ gm. of protein per kilo body weight is sufficient to maintain nitrogen equilibrium, provided the total caloric intake is great enough to supply the metabolic needs of the body. By the use of large quantities of fat they have been able to satisfy the total caloric requirement of the patients and keep them in nitrogen equilibrium on the small quantity of protein allotted.

The Fat Content. The pendulum of fat-feeding is now swinging again in the other direction. The present teaching is that a maximum of fat should be used within the limit of ketosis. This principle of high-fat feeding was considered a very dangerous procedure until Newburgh and Marsh[9] published their startling results with

diets high in fat. These results were soon explained by some interesting *in vitro* experiments performed by Shaffer,[10] in which he showed that when glucose was added to test tubes containing aceto-acetic acid in the presence of hydrogen peroxide, alkali, proper conditions of temperature, etc., aceto-acetic acid was rapidly oxidized. He found[11] that one molecule of glucose accomplished the disappearance of two molecules of aceto-acetic acid when the latter was present in excess. He, therefore, assumed that this "ketolytic" behavior of glucose *in vitro* was evidently analogous to the antiketogenic property of carbohydrate in preventing or abolishing ketonuria in the human subject. He cited numerous cases from the literature in which he calculated the ketogenic antiketogenic balance and found that if the total number of ketogenic molecules in the metabolic mixture did not exceed twice the number of ketolytic molecules, ketosis would be at a minimum. This is in keeping with clinical results obtained by Newburgh and Marsh[12] and Wilder and Winter,[13] although opposed by the views of Woodyatt[5] and those of Hubbard and Wright.[14] On the basis of a 1 to 1 ratio, *i.e.*, 1 molecule of glucose oxidizing 1 molecule of aceto-acetic acid, Woodyatt has suggested that if the ratio of fatty acid to glucose is greater than 1.5 to 1, acidosis will develop. Newburgh and Marsh[12] in a series of 190 cases produced no acidosis with diets containing a fatty acid to glucose ratio of 2.5 to 3 to 1. Thus it becomes evident that considerable quantities of fat can be used with safety.

The Total Caloric Content. In 1914 Allen introduced the principle of starvation in the treatment of diabetes. It soon became apparent that fasting was not only unpleasant and exhausting, but occasionally caused death. Such a procedure is unnecessary if one analyzes the metabolism during fast.

During fast, an individual does not cease to produce heat. Benedict[15] has shown that on the second day of a fast, a subject produced 1768 calories or 29.9 calories per kilogram and the individual was estimated to have catabolized 74.7 gm. of protein, 147.5 gm. of fat and 23.1 gm. of glycogen. Voit[16] has shown that a well-nourished dog which during starvation burned 96 gm. of body fat, burned 97 gm. when fed 100 gm. of fat. The fat ingested simply burned instead of body fat. Thus if a diabetic during fast reacts essentially as a non-diabetic individual, in the same state of nutrition, and if he weighs 60 kg., produces 1800 calories and in doing so burns 150 gm. of fat, the ingestion of an equal amount of fat should leave his metabolism in the same state as before. If this is true, why then should one ever use complete fasting for diabetics? The method of choice, then, is to feed diets high in fat, containing a sufficient number of calories to satisfy the basal requirement.

From the foregoing, one naturally concludes that the optimal diabetic diet should contain a minimum of carbohydrate, just

sufficient protein to maintain nitrogen equilibrium, the greatest amount of fat possible within the limit of ketosis and sufficient total calories to satisfy the basal requirement.

These requirements are admirably filled in the low-carbohydrate, low-protein, high-fat diets advocated by Newburgh and Marsh.[9] A list of the diets used are given in Table I showing the total glucose values and fatty acid to glucose ratios.

TABLE I.—NEWBURGH DIETS. HIGH-FAT DIETS SHOWING TOTAL GLUCOSE AND FATTY ACID GLUCOSE RATIOS.

	Protein.	Fat.	Carbohydrate.	Calories.	Total glucose.	Ratio FA/G.
No. I . .	20.51	87.62	14.6	929.0	34.65	2.5
No. II . .	28.75	138.42	20.31	1442.0	50.8	2.7
No. III . .	34.31	174.71	29.8	1828.8	67.2	2.5
No. IV . .	53.62	232.75	36.36	2454.6	90.7	2.6
ADDITIONAL HIGH-FAT DIETS IN USE AT THE GENERAL HOSPITAL.						
1 . . .	22.5	113.6	17.6	1182.8	42.0	2.6
2 . . .	25.5	125.5	19.1	1307.9	46.4	2.6
3 . . .	31.8	157.6	25.3	1646.8	59.5	2.6
4 . . .	38.0	183.0	32.0	1927.0	72.0	2.5
5 . . .	73.8	201.5	44.5	2273.8	107.5	2.0
6 . . .	65.4	241.7	50.4	2638.5	112.1	2.2
7 . . .	70.5	247.2	78.1	2819.2	143.7	1.7
8 . . .	74.1	248.0	110.2	2969.8	179.0	1.4

Our experience with such a dietary dates from April, 1922. The first case in our series G-1808 a man, aged thirty-seven years, entered the hospital February 27, 1922, complaining of polyuria, polydipsia and polyphagia. The duration of symptoms was one year. He had lost considerable weight, became weak, tired and impotent. Four weeks before entrance there was a general pruritus; one week before entrance edema of feet and ankles developed. On a regular house diet he eliminated 150 to 200 gm. of glucose in the urine with considerable acetone and diacetic acid. The Allen form of treatment was initiated with absolute starvation and the patient became sugar-free on the fifth day. The diet was gradually raised, using equal parts of protein and fat and small quantities of carbohydrate. After six weeks of treatment the diet consisted of 8 gm. of carbohydrate, 49 gm. of protein, 65 gm. of fat, 813 calories and resulted in the appearance of traces of sugar in the twenty-four-hour urinary specimen. In spite of the edema, which persisted, the patient lost 17 pounds in weight, became weaker and weaker until he could hardly stand on his feet. The necessity of increasing the caloric content of the diet became apparent, so, as a last resort, the high-fat diet was given with trepidation. The first diet given consisted

of 14.5 gm. of carbohydrate, 21 gm. of protein, 80 gm. of fat, 858 calories. On this diet he became sugar-free in two days, remained sugar-free for six days. During his remaining five weeks' stay in the hospital, the diet was gradually raised to 2100 calories, using similar proportions of fat, protein and carbohydrate, with the result that the patient's urine remained sugar- and ketone-free; he gained 12 pounds in weight in spite of loss of edema during treatment and left the hospital in excellent condition. Additional data are given in Table II. A subsequent history of this case was fortunately obtained just recently. The patient did splendidly for eight months gaining strength and 10 more pounds in weight. Four months ago he entered a boarding-house where it was considered troublesome to prepare his special diet. He became negligent, ate a regular diet and entered the hospital May 9, in diabetic coma.

TABLE II.—CASE SHOWING TRANSITION FROM ALLEN TO NEWBURGH TREATMENT.

Date, 1922.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds.	Remarks.
				C.	P.	F.	Cal.			
2/28	++++	+++	+++		Incomplete			....	118	
3/1 to 3/4	150–200	+++	+++		Regular diet					
3/4	99	+++	+++		Starvation			....	117.5	
3/5	19.2	+++	++		Starvation			.267	114.5	
3/6	15	+++	++		Starvation					
3/7	Trace	++	++		Starvation					
3/8	0	+	○		Starvation			.151	113	
3/9 to 3/19	0	+	○	8.0	16.8	8.0	106	....	116	Feet edematous.
3/19 to 4/13	0	○	○	5.0	42.5	25.0	415	....	113	Feet edematous.
4/13 to 4/23	Trace	○	○	8.0	49.0	65.0	813	....	109	Feet edematous.
4/23 to 4/28	0	○	○	14.5	21.0	80.0	858	....	101	Feet edematous.
4/28 to 5/28	0	○	○	21.6	33.5	149.8	1504	.15	.....	No edema.
5/28 to 6/4	0	○	○	27.9	42.0	173.0	1824	....	109	No edema.
6/4	0	○	○	50.2	43.4	191.2	2100	....	112	No edema.

The favorable result obtained in this case led us to try the high-fat diet in other diabetics. All cases that subsequently entered the hospital were immediately placed on a diet containing 18 to 20 gm. of protein, 12 to 15 gm. of carbohydrate, 85 to 90 gm. of fat, equivalent to 800 to 1000 calories. The patients remained on this diet until sugar-free for four to six days; the diets were then gradually increased until a maximum diet was reached which was within the patient's tolerance. In all, 52 cases have been treated in this fashion. Seventeen cases are presented in Table III to show the results obtained. On the initial diet, patients became sugar-free in from two to fourteen days; ketosis disappeared two to four

TABLE III

Case.	Sex.	Age at admission.	Probable duration of diabetes.	Body weight pounds.		Final.	Complications.	Initial diet, grams.				Urine.		Blood sugar, per cent.		Final diet, grams.			
				Before diabetes.	At admission.			C.	P.	F.	Cal.	Day sugar-free.	Day acetone-free.	On admission.	On discharge.	C.	P.	F.	Cal.
G–1808	M.	37	1 yr.	....	107	112	None	15.0	21.0	80.0	864	0	0	.267	.15	50.0	43	191	2091
G–5402	M.	49	3 mos.	145	111	108	None	15.0	21.0	87.0	927	11	12	.228	.14	36.0	53	233	2453
G–4982	F.	54	5 yrs.	185	130	125	None	22.0	22.0	90.0	986	14	18	.75	.18	31.0	29	143	1527
G–5294	M.	41	10 yrs.	230	195	190	Furuncles	15.0	21.0	80.0	864	7	14	.589	.295	28.0	36	147	1579
G–3514	F.	56	1 yr.	200	123	122	None	14.5	21.4	80.3	858	3	6	.33	.22	32.9	53	215	2285
G–5273	M.	27	1 yr.	....	147	147	None	22.0	22.0	90.0	986	3	0	.222	.08	41.0	58	273	2847
G–6181	M.	55	?	....	128	126	Infection	15.0	21.0	80.0	864	4	0	.18	....	36.0	53	233	2453
G–7331	M.	42	11 yrs.	230	192½	187	Furuncles	15.0	21.0	80.0	864	3	6	.4	.105	36.0	53	233	2453
G–5530	M.	44	4 yrs.	190	123½	117	None	14.6	20.5	87.6	929	6	14	.25	.16	40.0	60	244	2596
H–534	F.	49	2 yrs.	....	135	134	None	15.0	21.0	80.0	864	5	11	.35	.12	46.0	89	313	3357
H–1194	F.	49	6 mos.	....	....	....	None	12.0	27.0	92.0	984	4	10	.258	.13	36.0	53	233	2453
H–3103	F.	61	10 yrs.	211	146	144	Beginning gangrene	20.0	22.0	91.0	987	2	9	....	.103	30.0	34	174	1822
H–3025	F.	58	11 yrs.	186	126	125	None	15.0	21.0	82.0	882	3	2	.36	.18	30.0	34	176	1840
H–2976	F.	52	1 yr.	203	140	134½	Gangrene	20.0	22.5	91.0	989	4	0	.25	.167	36.0	54	237	2493
H–2977	F.	42	2 yrs.	230	184	178	None	20.0	23.0	91.0	991	4	14	.155	.114	36.0	54	237	2493
H–3107	M.	39	2 mos.	160	137½	134	None	15.0	21.0	80.0	864	4	9	.137	.09	36.0	54	232	2448
H–2723	F.	56	2 yrs.	200	118½	117	Gangrene	15.0	21.0	87.0	927	16	16	.223	.14	30.0	34	175	1831

days after freedom from glycosuria, the blood sugar dropped to normal level and there was definite clinical improvement. This list includes only cases admitted on the medical service who were known to follow the diet. It does not include cases of diabetic coma, nor are cases included which did not obey instructions during observation. In 2 cases a maximum diet of only 1500 calories could be given. The remainder of the cases were discharged upon diets containing over 1800 calories, the majority of these in the vicinity of 2400 calories.

Case Reports. Detailed reports of 5 cases are given to show the effects of the high-fat diet.

CASE I.—M. D., H–1194, female, aged forty-nine years, entered the hospital February 26, 1923, complaining of abdominal trouble. She was not aware that she had diabetes, which was discovered during the routine examination. This patient was placed on a diet containing 12.3 gm. of carbohydrate, 27.2 gm. of protein, 92.7 gm. of fat, 994 calories, and became sugar-free in two days. Patient remained sugar-free as diet was gradually increased to 2456 calories with a fat content of 232.7 gm. The blood sugar dropped from .258 to .147 per cent. For further details see Table IV.

TABLE IV.

Date, 1923.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Total, G.	Ratio FA/G.	Blood sugar, per cent.	Weight in pounds.
				C.	P.	F.	Cal.				
2/26	65.8	+	O	Incomplete							
2/27	2.37	O	O	12.3	27.2	92.7	994	37	2.6		
2/28	0	Trace	O	14.6	24.7	94.0	1003	38	2.5	.258	
3/1	0	Trace	O	20.3	22.6	90.4	988	42	2.1	....	169
3/2	0	O	O	14.8	25.3	86.2	935	38	2.3		
3/3	0	O	O	15.3	22.6	96.6	1021	38	2.5		
3/4	0	O	O	20.3	28.7	138.4	1423	51	2.7		
3/5	0	O	O	20.3	28.7	138.4	1423	51	2.7	....	171
3/6	0	O	O	20.3	28.7	138.4	1423	51	2.7		
3/7	0	O	O	20.3	28.7	138.4	1423	51	2.7		
3/8	0	O	O	29.8	34.3	174.7	1826	67	2.6		
3/9	0	O	O	29.8	34.3	174.7	1826	67	2.6		
3/10	0	O	O	29.8	34.3	174.7	1826	67	2.6	....	169
3/11	0	O	O	36.3	53.6	232.7	2456	90	2.5		
3/12	0	O	O	36.3	53.6	232.7	2456	90	2.5		
3 13	0	O	O	36.3	53.6	232.7	2456	90	2.5	.147	
3/14	0	O	O	36.3	53.6	232.7	2456	90	2.5	....	170
3/15	0	O	O	36.3	53.6	232.7	2456	90	2.5		

CASE II.—S. D., G–4982, female, aged fifty-four years, entered the hospital August 15, 1922, complaining of painful and swollen feet. Sugar was found in her urine five years previously; she had lost 50 pounds in weight. Considerable sugar, acetone and diacetic acid were found in the urine. Blood sugar was 0.75 per cent, alkali reserve 44. On a diet containing 22.3 gm. carbohydrate, 22.3 gm. protein, 90.3 gm. fat, 991 calories, the patient became sugar-free in

fourteen days. The diet was raised to 1526 calories which seemed to be all that she could tolerate. See Table V.

TABLE V.

Date.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Total G.	Ratio FA/G.	Blood sugar, per cent.
				C.	P.	F.	Cal.			
7/16/22	++++	+++	....	Incomplete						
7/17/22	25.0	+++	+++	Regular diet				200?		
7/18/22	165.0	+++	+++	Regular diet				200?	...	.75
7/19/22	56.0	+++	+++	22.3	22.3	90.3	991	44.2	2.0	
7/20/22	21.4	+++	+++	22.3	22.3	90.3	991	44.2	2.0	
7/21/22	11.3	+++	+++	22.3	22.3	90.3	991	44.2	2.0	
7/22/22	13.8	+++	++	22.3	22.3	90.3	991	44.2	2.0	
7/23/22	19.5	++	+	22.3	22.3	90.3	991	44.2	2.0	
7/24/22	7.0	+	+	22.3	22.3	90.3	991	44.2	2.0	
7/25/22	6.5	+	Trace	22.3	22.3	90.3	991	44.2	2.0	
7/26/22	4.0	Trace	Trace	22.3	22.3	90.3	991	44.2	2.0	
7/27/22	14.9	Trace	0	22.3	22.3	90.3	991	44.2	2.0	
7/28/22	2.1	0	0	22.3	22.3	90.3	991	44.2	2.0	
7/29/22	6.5	0	0	22.3	22.3	90.3	991	44.2	2.0	
7/30/22	Trace	0	0	22.3	22.3	90.3	991	44.2	2.0	
7/31/22	Trace	0	0	22.3	22.3	90.3	991	44.2	2.0	
8/1/22	2.0	0	0	22.3	22.3	90.3	991	44.2	2.0	
8/2/22	0	0	0	22.3	22.3	90.3	991	44.2	2.0	
8/3/22	0	0	0	22.3	22.3	90.3	991	44.2	2.0	
8/4/22	0	0	0	30.6	29.4	142.9	1526	61.9	2.2	
8/5/22	0	0	0	30.6	29.4	142.9	1526	61.9	2.2	
8/6/22	0	0	0	30.6	29.4	142.9	1526	61.9	2.2	.18
8/7/22	0	0	0	30.6	29.4	142.9	1526	61.9	2.2	

CASE III.—J. W., G–5530, male, aged forty-four years, who had had diabetes for four and a half years, entered the hospital complaining of thirst, polyuria, polyphagia, weakness and numbness of extremities. Former weight 190 pounds; present weight 125 pounds. Considerable glucose, acetone and diacetic acid were found in the urine. On a diet containing 14.6 gm. of carbohydrate, 20.5 gm. of protein, 87.6 gm. of fat and 929 calories, the patient became sugar-free on the sixth day. The acetone and diacetic acid disappeared a day later. He responded nicely to the usual dietary increases until a dose of neosalvarsan was given for his lues. The following day sugar, acetone and diacetic acid appeared in the urine. The diet was again decreased, but it was not until the second day of a starvation diet that the patient became sugar-free, on the eighteenth day after the reappearance of sugar in the urine. Following this incident the patient made an uneventful partial recovery. See Table VI.

CASE IV.—W. R., G–5402, male, aged forty-nine years, entered the hospital complaining of the usual diabetic symptoms of three months' duration. During the past four weeks he had lost 34 pounds in weight. On a diet similar to the one stated in the preceding case, the patient became sugar-free on the eleventh day. Acetone and diacetic reactions of the urine were negative about a week later. This patient responded nicely to dietary increases up to 2456 calories. The blood sugar dropped from 0.228 per cent to 0,144 per cent. See Table VII.

TABLE VI.—CASE SHOWING EFFECT OF NEOSALVARSAN ON CARBOHYDRATE TOLERANCE.

Date, 1922.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds	Remarks.
				C.	P.	F.	Cal.			
8/10	44.6	+++	+++	14.6	20.5	87.6	929	....	123½	
8/11	40.9	+++	++	14.6	20.5	87.6	929	.222		
8/12	23.3	++	+	14.6	20.5	87.6	929			
8/13	13.0	+	+	14.6	20.5	87.6	929			
8/14	4.3	+	+	14.6	20.5	87.6	929			
8/15 to 8/18	0	+	+	14.6	20.5	87.6	929			
8/18 to 8/21	0	0	0	27.8	29.7	141.2	1415	.230		
8/21 to 8/23	0	0	0	26.2	34.2	176.0	1827			
8/23	0	0	0	26.2	34.2	176.0	1827	.255	....	.9 neosalvarsan given.
8/24	15.4	+	+	26.2	34.2	176.0	1827	....	....	Arm painful and swollen.
8/25	13.4	+	+	26.2	34.2	176.0	1827	....	....	Arm painful and swollen.
8/26 to 8/31	15 to 22	+	+	20.3	28.7	138.0	1438	....	....	Arm painful and swollen.
8/31 to 9/9	10 to 15	+	+	14.6	20.5	87.6	929	....	....	Arm painful and swollen.
9/9	+++	+	+		Starvation					
9/10	+	+	+		Starvation			....	....	Arm improved
9/11	0	+	+		Starvation					
9/12 to 9/16	0	0	0	14.6	20.5	87.6	929			
9/16 to 9/19	0	0	0	20.3	28.7	138.0	1438			
9 19 to 9/22	0	0	0	26.3	34.2	176.0	1827			
9/22 to 9/25	0	0	0	36.3	53.6	232.7	2456	.169		

TABLE VII.

Date.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Total G.	Ratio FA/G.	Blood sugar, per cent.	Weight of patient, lbs.
				C.	P.	F.	Cal.				
8/3/22	45.6	+++	+++		Incomplete						
8/4/22	12.6	+++	+++	14.6	20.5	87.6	929.0	35.3	2.5	.228	
8/5/22	65.1	+++	+++	14.6	20.5	87.6	929.0	35.3	2.5		
8/6/22	21.4	+++	+++	14.6	20.5	87.6	929.0	35.3	2.5		
8/7/22	22.8	+++	+++	14.6	20.5	87.6	929.0	35.3	2.5		
8/8/22	14.8	+++	+++	14.6	20.5	87.6	929.0	35.3	2.5	....	110
8/9/22	10.6	+++	+++	14.6	20.5	87.6	929.0	35.3	2.5	....	110
8/10/22	21.8	+++	+++	14.6	20.5	87.6	929.0	35.3	2.5	....	110
8/11/22	13.9	+++	+++	14.6	20.5	87.6	929.0	35.3	2.5		
8/12/22	13.4	++	++	14.6	20.5	87.6	929.0	35.3	2.5		
8/13/22	7.0	++	+	14.6	20.5	87.6	929.0	35.3	2.5		
8/14/22	0	+	–	14.6	20.5	87.6	929.0	35.3	2.5		
8/15/22	0	–	–	14.6	20.5	87.6	929.0	35.3	2.5	....	110
8/16/22	0	–	–	14.6	20.5	87.6	929.0	35.3	2.5	....	109½
8/17/22	0	–	–	27.8	29.7	141.2	1415.0	59.1	2.3	....	109
8/18/22	0	+	+	27.8	29.7	141.2	1415.0	59.1	2.3	....	108
8/19/22	0	+	+	27.8	29.7	141.2	1415.0	59.1	2.3		
8/20/22	0	–	–	26.2	34.2	176.2	1827.7	63.6	2.7		
8/21/22	0	Trace	Trace	26.2	34.2	176.2	1827.7	63.6	2.7	....	108
8/22/22	0	–	–	26.2	34.2	176.2	1827.7	63.6	2.7		
8/23/22	0	–	–	26.2	34.2	176.2	1827.7	63.6	2.7	.144	108
8/24/22	0	–	–	26.2	34.2	176.2	1827.7	63.6	2.7		
8/25/22	0	–	–	26.2	34.2	176.2	1827.7	63.6	2.7	....	107
8/26/22	0	–	–	36.3	53.6	232.7	2456.0	90.6	2.5		
8/27/22	0	–	–	36.3	53.6	232.7	2456.0	90.6	2.5	....	106½
8/28/22	0	–	–	36.3	53.6	232.7	2456.0	90.6	2.5	....	107
8/29/22	0	–	–	36.3	53.6	232.7	2456.0	90.6	2.5	....	107½
8/30/22	0	–	–	36.3	53.6	232.7	2456.0	90.6	2.5	....	107½

CASE V.—L. E., H-2976, female, aged fifty-two years, entered the hospital complaining of diabetes, complicated by gangrene of the left great toe. The duration of diabetes was not known. She had lost 50 pounds in weight during the past two years. After receiving the 929 calories diet she became sugar-free on the fourth day. The gangrenous toe was amputated May 12, 1923. Remainder of patient's stay in hospital was uneventful. See Table VIII.

TABLE VIII.—CASE WITH GANGRENE OF GREAT TOE; IMPROVED UNDER TREATMENT. AMPUTATION.

Date, 1923.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds
				C.	P.	F.	Cal.		
4/21	32.8	—	—	14.6	20.5	87.62	929.0	....	139½
4/22	14.49	—	—	14.6	20.5	87.62	929.0		
4/23	12.0	—	—	14.6	20.5	87.62	929.0		
4/24	—	—	—	14.6	20.5	87.62	929.0		
4/25	—	—	—	22.6	20.3	90.8	988.8	.25	139½
4/26	—	—	—	22.6	20.3	90.8	988.8		
4/27	—	—	—	27.82	29.70	141.27	1415.7		
4/28	—	—	—	27.82	29.70	141.27	1415.7		
4/29	—	—	—	27.82	29.70	141.27	1415.7		
4/30	—	—	—	27.82	29.70	141.27	1415.7		
5/1	—	—	—	27.82	29.70	141.27	1415.7		
5/2	—	—	—	27.82	29.70	141.27	1415.7		
5/3	—	—	—	27.82	29.70	141.27	1415.7		
5/4	—	—	—	26.24	34.22	176.21	1827.7		
5/5	—	—	—	26.24	34.22	176.21	1827.7		
5/6	—	—	—	26.24	34.22	176.21	1827.7	....	134½
5/7	—	—	—	26.24	34.22	176.21	1827.7		
5/8	—	—	—	25.03	34.78	167.10	1705.2	.167	
5/9	—	—	—	36.36	53.62	232.75	2456.6		
5/9 to 6/9	—	—	—	36.36	53.62	232.75	2456.6	.146	

Thus the remarkable improvement noticed under this form of treatment has never caused us to regret the change from the former starvation, severe undernutrition style of treatment to the present high-fat feeding.

When insulin became available the treatment was modified as follows: Comatose and precomatose patients received insulin immediately. The others were placed on diets which were 20 per cent over the basal requirement. This included 10 per cent for the specific dynamic action of food and 10 per cent for slight activity in bed. For clinical purposes about 30 calories per kilo sufficed. For example, a patient weighing 50 kilos would receive a diet containing 1500 calories. The high-fat diets described above were used. Patients remained in bed on this diet for a week while daily blood and urine examinations were made. Those who became sugar-free were advised to continue the dietetic treatment. The others were given insulin. To obtain the maximum effect from insulin at the time when food absorption was at its height, the doses were given fifteen to thirty minutes before a meal. Subcutaneous adminis-

tration was the method of choice. During the experimental stages of investigation small doses of insulin were given twice daily, before breakfast and supper, and the effect upon the blood sugar was determined. By noticing the amount of additional glucose utilized by the administration of definite quantities of insulin, it soon became apparent that one unit of insulin provided for the utilization of approximately 2 gm. of glucose. In subsequent cases the dosage of insulin was regulated accordingly, so that after a week's observation the amount of insulin required in a given case could be predicted with some accuracy.

There is a direct relationship between the amount of insulin given and the quantity of glucose utilized. Thus it is advantageous to construct a diet which contains a maximum number of calories with a minimal amount of available glucose. If the high-fat diet used in these experiments is carefully analyzed, one observes that there are 28 calories present in the diet for each gram of available glucose. A diet of 1700 calories, for example, contains 60 grams of available glucose. Comparing this with an ordinary Allen diet of the same caloric value containing 100 gm. each of protein, fat and carbohydrate one finds a total glucose content of 168 grams or 10 calories for each gram of glucose. A total diabetic placed on each of these diets would require 30 units of insulin on the former, 84 units on the latter, a difference of 54 units. The optimal diet, then, becomes economical for two reasons. In the first place, it enables the ordinary case of diabetes with a fair glucose tolerance to handle a diet sufficient in number of calories and compatible with earning a livelihood in which the amount of activity required is not excessive. In the second place, if the patient's glucose tolerance is not sufficient to maintain him on an adequate diet, fewer number of insulin units will be required with less financial strain on the patient.

During the last three to four days of the preliminary observation the morning blood sugar reaches a fairly constant level and the amount of glucose excreted in twenty-four hours is also fairly constant. This amount of glucose, divided by 2, represents the number of insulin units administered in twenty-four hours. If small quantities of glucose, 2 to 5 grams are still eliminated during the twenty-four-hour period, the following method of procedure is used: Two-hourly urine examinations for sugar are made to determine at which time during the day glucose is escaping. The dose of insulin is either increased or properly timed to eliminate this period of glycosuria. Attempts are made to keep the urine sugar-free and the blood sugar at the normal level. Five to 7 additional units of insulin are usually required to bring the blood sugar down to the normal level after the urine is sugar-free.

Results. Up to the present time 15 cases have been treated with insulin. The most striking results have been obtained in children,

young adults and uncomplicated cases of coma. During insulin treatment the first signs of improvement noted are symptomatic. One patient stated that he had a feeling of well-being after each injection. If proper doses of insulin are given, the urine becomes sugar-free, the blood sugar drops to the normal level, ketones disappear from the urine and the patients improve clinically. If the diet given is over the basal calorie requirement, the patients gain rapidly in weight. One patient who had lost 10 pounds in weight during several months regained the weight lost in a week's time. The average severe case of diabetes requires about 20 to 30 units of insulin daily to keep him sugar-free on a diet containing 2400 calories.

The following case illustrates some of the points discussed:

A. E., H–2975, male, aged sixty years, while attempting to pass an insurance examination seven years ago, was told that he had diabetes. During the past two years he had been suffering from excessive thirst, polyuria and loss of weight (30 pounds during past year). On entrance into hospital considerable sugar, acetone and diacetic acid were found in the urine. On a diet containing 20 gm. of carbohydrate, 28 gm. of protein, 140 gm. of fat, 1452 calories, the patient eliminated from 10 to 18 gm. of glucose during twenty-four hours. The diet was increased to 1652 calories, thus increasing the total glucose by 10 gm. and 10 units of insulin were given subcutaneously in one dose before breakfast. On the third day the patient became sugar-free; the acetone and diacetic acid disappeared five days later. The diet was increased first to 1825 calories and then to 2453 calories. The patient remained sugar-free. Blood sugar 0.18 on admission dropped to 0.105 and then rose to 0.15 just before discharge. See Table IX.

TABLE IX.

Date, 1923.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds.	Insulin units.
				C.	P.	F.	Cal.			
4/22	+++	+++	+++	Incomplete				.18	109	
4/23	18.0	+++	+++	20.0	28.0	140	1452	....	109	
4/24	13.4	+++	+++	20.0	28.0	140	1452	....	109	
4/25	10.0	++	++	20.0	28.0	140	1452	....	109	
4/26	18.5	++	++	20.0	28.0	140	1452	....	108	
4/27	15.4	++	++	23.0	39.0	156	....	....	105	
4/28	9.6	+	+	23.0	39.0	156	1652	....	105	10
4/29	5.4	+	+	23.0	39.0	156	1652	....	106	10
4/30	0	+	+	23.0	39.0	156	1652	....	106	10
5/1	0	+	+	23.0	39.0	156	1652	....	107	10
5/2	0	+	+	23.0	39.0	156	1652	....	106	10
5/3	0	+	+	23.0	39.0	156	1652	....	105	10
5/4	0	–	–	26.2	34.2	176	1825	....	105	10
5/5	0	–	–	26.2	34.2	176	1825	....	105	10
5/6	0	–	–	26.2	34.2	176	1825	....	106	10
5/7	0	–	–	26.2	34.2	176	1825	.105	106	10
5/8	0	–	–	36.0	53.0	233	2453	....	106	10
5/9	0	–	–	36.0	53.0	233	2453	....	106	10
5/10	0	–	–	36.0	53.0	233	2453	.15	106	10

TABLE X.

Date, 1922–23	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds.	Insulin units.	Remarks.
				C.	P.	F.	Cal.				
11/22 to 12/1	30–36	+++	+++	14.4	21 6	82.4	850	.258	91	0	
12/1 to 12/12	35–45	+++	+++	34.3	60.0	166.0	1879	.266	101	0	
12/12	9.1	+++	+++	34.3	60.0	166.0	1879	....	101	80	
12/13	0	++	++	34.3	60.0	166.0	1879	....	102	120	
12/14	0	++	++	34.3	60.0	166.0	1879	.085	102	80	
12/15	12.4	++	++	34.3	60.0	166.0	1879	....	102	0	
12/16 to 12/20	25–38	+++	+++	34.3	60.0	166.0	1897	....	102	0	
12/20	31.7	+++	+++	34.3	60.0	166.0	1879	....	102	325	By mouth
12/21 to 12/30	20–25	+++	+++	34.3	60.0	166.0	1879	.289	100	50	
12/30	44.0	+++	+++	34.3	60.0	166.0	1879	....	99	100	By rectum
12/30 to 1/8	18–25	+++	+	34.3	60.0	166.0	1879	....	95	50	
1/8	15.0	+++	–	34.3	60.0	166.0	1879	....	95	50	
1/9	17.7	++	–	34.3	60.0	166.0	1879	....	95	50	
1/10	3.2	+	–	34.3	60.0	166.0	1879	....	95	50	
1/11	0	+	–	34.3	60.0	166.0	1879	....	95	50	
1/12	0	+	–	34.3	60.0	166.0	1879	....	95	60	
1/13	0	+	–	34.3	60.0	166.0	1879	....	95	50	
1/14 to 1/16	0	+	–	34.3	60.0	166.0	1879	....	95	40	
1/16	0	+	–	34.3	60.0	166.0	1879	....	95½	30	
1/17 to 1/20	0	+	–	34.3	60.0	166.0	1879	.24	96	20	
1/20	0	+	–	34.3	60.0	166.0	1879	....	96	10	
1/21	Trace	+	–	34.3	60.0	166.0	1879	....	96	10	
1/22	2.19	+	–	34.3	60.0	166.0	1879	....	96	20	
1/23	0	0	–	34.3	60.0	166.0	1879	....	96	0	
1/24 to 1/28	Trace	+	–	34.3	60.0	166.0	1879	....	96	0	
1/28 to 2/10	2.3–20	+	–	34.3	60.0	166.0	1879	....	96	0	Insulin by mouth.

TABLE XI.

Date, 1923.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds.	Insulin units.
				C.	P.	F.	Cal.			
4/14	41.0	+++	++	38	48.5	129	1507	.37	104	20
4/15	25.2	+++	++	38	48.5	129	1507	....	105	20
4/16	55.0	+++	++	38	48.5	129	1507	....	...	30
4/17	22.8	+++	++	38	48.5	129	1507	....	106	30
4/18	24.0	++	+	38	48.5	129	1507	....	107	30
4/19	22.8	++	+	38	48.5	129	1507	....	110	50
4/20	16.2	++	+	38	48.5	129	1507	....	111	50
4/21	12.0	++	+	38	48.5	129	1507	....	112	50
4/22	8.0	++	+	38	48.5	129	1507	....	113	50
4/23	6.9	++	+	38	48.5	129	1507	....	114	50
4/25	0	+	+	38	48.5	129	1507	....	114	50
4/26	0	Trace	0	38	48.5	129	1507	.20	114	35
4/27	0	Trace	0	50	60.0	175	2015	....	114	35
4/28	0	0	0	50	60.0	175	2015	....	113	35
4/29	0	0	0	50	60.0	175	2015	....	113	35
4/30	0	0	0	50	60.0	175	2015	....	113	35
5/1	0	0	0	50	60.0	175	2015	....	113	35
5/2	0	0	0	50	60.0	175	2015	....	113	35
5/3	0	0	0	50	60.0	175	2015	....	113	35
5/4	0	0	0	50	60.0	175	2015	....	114	30
5/5	0	0	0	50	60.0	175	2015	....	114	30
5/6	0	0	0	50	60.0	175	2015	....	114	30
5/7	0	0	0	50	60.0	175	2015	.167	114	30
5/8	0	0	0	50	60.0	175	2015	....	114	30
5/9	0	0	0	50	60.0	175	2015	....	114	30

The Glucose Tolerance. In all of our cases during the short period of observation there was a noticeable increase in the glucose tolerance as evidenced by the decrease in insulin necessary to maintain patients aglycosuric. In 1 case the dose was decreased from 120 units per day to 20 units per day on an 1800 caloric diet (Table X). In another case the dosage was decreased from 50 to 20 units on the same diet (Table XI). In 2 cases sufficient tolerance was regained so that insulin was discontinued and the patient discharged on an adequate diet.

Treatment of Coma Cases. No definite plan of treatment of coma is as yet available. Banting, Campbell and Fletcher[4] in a recent communication were not prepared to lay down definite rules for the management of diabetics in coma.

The plan of treatment in vogue at the Cincinnati General Hospital is briefly as follows: Patients brought into the hospital in coma are covered with warm blankets and surrounded by hot-water bottles. Blood is taken for examination and 50 units of insulin administered intravenously in 200 cc of 15 per cent glucose. Blood is examined for sugar and alkali reserve before and several hours after injection of insulin. Usually in three to four hours clinical improvement is noted, sometimes to the point of returning consciousness. Large doses of insulin are continued hypodermatically together with glucose intravenously or by mouth; the latter method is the one of choice, if the patient is conscious. Inasmuch as the coma is due to the products of disturbed fat metabolism, the foremost concern in the early treatment is the prevention of accumulation of these products. Large quantities of glucose are given with large doses of insulin to create a tremendous metabolic fire, so that the further accumulation of ketone bodies ceases. The ketone bodies already present are washed out with large quantities of fluid and alkali. Fluids are given by every avenue of approach and patients in their desiccated state will take up 5000 to 6000 cc in twenty-four hours. Alkalies are given in the form of sodium bicarbonate per rectum or intravenously. As soon as the patient emerges from coma, measured quantities of food are given with insulin. The amounts of insulin required at this stage are larger than ordinarily required; perhaps one or more units per gram of glucose. In the uncomplicated cases of coma the results obtained are miraculous. Within three to four hours the patient begins to respond to painful stimuli. Soon after, the blood alkali reserve commences to rise. In a short time the ketone bodies disappear from the urine and the blood sugar falls. At this stage the treatment must be accurately checked up by laboratory data. Fall in the blood sugar and absence of glycosuria are indications for the administration of more glucose. Failure of a rise in the alkali reserve is indication that more insulin is required.

Five cases of coma have been treated at the Cincinnati General Hospital, death occurring in three. In each of these 3 cases, at the time of death, the blood sugar was normal or only slightly above the normal and the urine was sugar-free. One case died of uremia, 1 died of a multiplicity of complications, and 1 case entered the house in coma on two occasions, each time was resuscitated and finally died a month after the second admission with bronchopneumonia. Necropsies were obtained in all the cases. In the 2 remaining cases, without complications, the recovery was easy and uneventful.

One case, a man, aged thirty-eight years, entered the hospital at 4 P.M. May 9, 1923, complaining of general weakness and shortness of breath. Breathing was Kussmaul in type. There was a cherry-red cyanosis to lips and nail beds. At 7 P.M., three hours later, the patient was in a semistuporous condition. The reflexes were absent. He did not respond to the prick of a pin. There was a marked general desiccation. Pulse was rapid, thumping, irregular in rhythm. Respiratory rate was 30. Extreme air-hunger was present. A sickening fruity odor of breath was present; 1025 cc of urine passed on entrance, contained 51 gm. of glucose, some albumin, considerable quantities of acetone and diacetic acid. Blood sugar was 0.625, alkali reserve 26. Swallowing reflex was fortunately still present, so that fluids could be forced by mouth. During preinsulin days, such a case never recovered.

Treatment. Fifty units of insulin were given hypodermatically at 8 P.M., followed by 100 cc of 5 per cent glucose solution every half hour for four hours and then every hour for the next twenty hours. Five grams of sodium bicarbonate dissolved in 120 cc of water was forced hourly for twenty-four hours. Fifty units of insulin was again given at midnight. During the first twenty-four hours the patient received 100 units of insulin, 140 gm. of glucose, 120 gm. of sodium bicarbonate and 5000 cc of fluid.

The following morning, the blood sugar was 0.215; alkali reserve was 50. The patient was conscious, Kussmaul breathing had disappeared and the general appearance was greatly improved. Considerable quantities of glucose were present in the urine but no diacetic acid was found. Thirty-six hours after admission the patient was sitting up in bed reading a newspaper. An 1800 caloric diet was then started with 20 units of insulin per day. The patient is now doing nicely. This patient is the individual mentioned earlier in this report who was the first case placed on the high-fat régime. His previous tolerance before leaving the hospital was established at 2200 calories with a total glucose content of 78. We will have occasion to study this case again and determine the effect of the precipitation of coma due to dietary excess on the glucose tolerance. See Table XII.

TABLE XII.—CASE OF DIABETIC COMA.

Date, 1923.	Time.	Sugar in urine.	Acetone.	Diacetic acid.	Blood sugar.	Alk. reserve.	Diet.	Insulin units.	Remarks.
5/9	8 P.M.	++++	++++	++++	.65	26	5 per cent glucose	50	Dyspnea, stupor cherry-red cyanosis, lessened sensibilities, diminished reflexes.
	12 M.	.....	.....	.....	....	..	5 per cent glucose	50	Less dyspnea.
5/10	8 A.M.	++++	++	−	.215	50	5 per cent glucose	0	Marked improvement.
5/11	8 A.M.	++++	+	−	.265	52	1826 calories high-fat	20	Bright and cheery, reading newspaper.
5/12	8 A.M.	○	−	−	....	..	Same diet	20	Feeling well.
5/13	8 A.M.	○	−	−	....	..	Same diet	20	Feeling well.
5/14	8 A.M.	++	+	−	....	..	Same diet	20	Feeling well.
5/15	8 A.M.	○	−	−	....	..	Same diet	20	Up and about.
5/16	8 A.M.	○	−	−	....	..	Same diet	20	Up and about.
5/17	8 A.M.	○	−	−	.243	..	Same diet	20	Up and about.

Hypoglycemic Reactions. In the treatment of cases of diabetes with insulin an occasional reaction may follow a fall in the blood sugar to below the normal level (hypoglycemia). According to Banting, the occurrence of this reaction depends on the rapidity of the fall as well as the per cent of the blood sugar. This may happen in spite of the extreme care exerted in controlling insulin administration by careful laboratory work. In a large diabetic clinic such reactions occur frequently. Campbell, at the recent meeting of the Society for Clinical Investigation at Atlantic City, reported as follows: When the blood sugar falls to 0.08 to 0.07 per cent there is a feeling of nervousness or uneasiness; patients complain of hunger and weakness; at 0.07 to 0.05 per cent there is always a profuse sweat; between 0.05 and 0.04 per cent there is delirium, excitement, sensory and motor aphasia, delusions, dysarthia and a bradycardia; at 0.035 per cent there is unconsciousness, lost or increased reflexes, increased muscle tonus, tremor. In our series we can only report a single occurrence of a hypoglycemic reaction.

A woman, aged fifty-five years, entered the hospital for the second time in diabetic coma. She was resuscitated by the treatment described above and finally placed on a diet controlled by 45 units of insulin per day. On the day that the reaction occurred the patient failed to eat the entire quantity of food given. The patient was constantly complaining of a cold feeling in her neck, headache and a burning sensation in the stomach. At 7 P.M., she suddenly appeared very stuporous. She was lying on her side, eyes wide open, facial expression blank. When asked questions, she mumbled unintelligibly. She failed to recognize her husband who was sitting

at the bedside. Respirations were quiet, deep and regular. Pulse was slow, good volume and tension, rhythm regular. Blood-pressure was systolic 140, diastolic 80. Body was flaccid. Pupils were equal, normal size, reacted to light. The left face twitched. At 8 P.M. coma had deepened. The arms and legs began to twitch. Right arm was moderately spastic. Knee-jerks were equal but sluggish. Biceps- and radial-jerks were equal and active. Plantar signs were normal. Pupils equal and reacted to light. Patient did not respond to painful stimuli. During examination there were rhythmical contractions of the diaphragm simulating attempts to retch. The blood sugar was 0.032 per cent, alkali reserve 73.

At 8.25 P.M. injection of 15 per cent glucose was begun intravenously. Within two minutes the patient opened her eyes and recognized her husband. Five minutes later there was a violent reaction; patient screamed, cried and struggled fiercely. The remainder of glucose was given with some difficulty, two persons being required to restrain patient. Morphine sulphate, gr. $\frac{1}{6}$, was given hypodermically. Patient gradually quieted down during the next ten minutes. Blood sugar fifteen minutes after glucose administration was 0.276 per cent, alkali reserve 70. The following day the patient was very comfortable. The blood sugar was 0.25 per cent, alkali reserve 64.

These hypoglycemic reactions can be easily relieved by administration of 10 to 20 gm. of glucose in a glass of orangeade.

Recovery is immediate. When the patient is unconscious 1 cc of adrenalin (1 to 1000) can be given intramuscularly followed by glucose per mouth. If the patient is not conscious enough to swallow glucose, subcutaneous and intravenous or per rectal administration can be used.

Conclusions. 1. The most important feature in the management of diabetics is the dietetic treatment.

2. The optimal diabetic diet should contain a minimum of carbohydrate, just sufficient protein to maintain nitrogen equilibrium, the greatest amount of fat possible within the limit of ketosis and sufficient total calories to satisfy the basal requirement.

3. The efficacy of such a diet is borne out by the clinical results obtained.

4. Such a diet is economical for two reasons: First, the diabetic with the glucose tolerance of 50 or more grams can be maintained on a diet sufficient in total number of calories to be compatible with earning a livelihood in which the amount of activity required is not excessive; secondly, the diabetic with an insufficient glucose tolerance can be maintained on an adequate diet with fewer number of insulin units and thereby less financial drain.

5. Insulin is a wonderful adjunct in the treatment of severe cases of diabetes.

6. Insulin is a specific in the treatment of uncomplicated cases of diabetic coma.

7. A treatment for cases in diabetic coma is presented.

8. Hypoglycemic reactions should be avoided but can be easily remedied when they occur.

NOTE.—The author wishes to express his most sincere thanks to Dr. Roger S. Morris for the privilege of working with insulin and for his interest in directing the investigation during its course. The insulin used was supplied gratis to the Medical Clinic by the Eli Lilly Company from November 1, 1922 to January 16, 1923. Thereafter it was bought from the Lilly Company by the hospital, which now has accumulated a special fund for the purpose, due to generous Cincinnatians and Cincinnati Organizations.

The cases studied were those which entered the Medical Service. One case from the Pediatric Service is presented by the courtesy of Dr. Kenneth Blackfan. After November 1, 1922, the cases entered the service of Dr. Mark A. Brown, to whom the author is grateful for numerous suggestions.

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POSTOPERATIVE MASSIVE PULMONARY COLLAPSE AND DROWNED LUNG.*

By Simon S. Leopold, M.D.,
PHILADELPHIA, PA.

The importance of postoperative pulmonary complications is appreciated, when it is realized that irrespective of the operation, or the anesthetic, one person in every fifty operated upon will develop some postoperative pulmonary complication.[1]

It is my purpose to consider only one of these: the condition commonly called Massive Collapse of the Lung.

Thirty-three years ago, William Pasteur[2] recognized and described massive pulmonary collapse found postmortem in fatal cases of diphtheria. He believed that this condition resulted from diaphragmatic paralysis. Five years later, he described its symptoms and physical findings in patients who had postdiphtheritic multiple paralysis.[3] In 1908, Pasteur, in the Bradshaw lecture,[4] first described massive pulmonary collapse occurring as a postoperative complication. This, and three subsequent publications, in 1910,[5] 1911[6] and 1914,[7] carefully and fully described this postoperative complication, and established it, as a not uncommon clinical entity. His contributions furnished the impetus for many others to record similar cases, which since that time, have appeared in increasing numbers in the literature and in the diagnoses of hospital records.

Many authors have differed greatly from Pasteur, as to the mechanism whereby postoperative pulmonary collapse is produced, but none have been able either to modify or amplify the clinical picture. His work is all the more noteworthy in that his early observations were, by necessity, unaided by the roentgen-ray or fluoroscope.

The four patients with so-called postoperative massive collapse of the lung whom I have been privileged to study, were observed at the Base Hospital at Camp Dix, New Jersey, during the time when it was my duty to see, in consultation with the Surgical Service, the cases of postoperative pulmonary complications.

It is remarkable, I think, that all of them were encountered within a period of sixteen days. Either this is a coincidence or a confession that many were overlooked, the latter probably being the correct interpretation. Perhaps this will serve as a plea for others to remember that this is not a rare condition and to keep it in mind when called upon to see cases of postoperative pneumonia, some of which surely will be found to belong to this group. It is interesting in this connection to note that Pasteur,[7] writing in the *British Journal of Surgery* in 1914, states: "The surgical records

* Read before the John Morgan Society, April, 6, 1923.

of the Middlesex Hospital furnished no examples of massive collapse, before 1908, when I first drew attention to it. Since then, there has been a gradual increase in the number of cases, and a corresponding decrease in those of postoperative pneumonia."

Cutler and Hunt[8] studied the postoperative pulmonary complications at the Peter Bent Brigham Hospital in 1919, and again in 1920,[9] in which year 63 pulmonary complications in 1604 surgical cases were found. The authors stated that no cases of massive collapse were noted in either survey.

Whipple,[10] who states that his interest in postoperative pulmonary complications was first aroused by unusual findings in thoracic roentgen-ray studies of patients having unexplained rises of temperature on the first or second postoperative days, studied the pulmonary complications which occurred at the Presbyterian Hospital in New York, under the title of "Postoperative Pneumonitis." He reported 97 postoperative pulmonary complications. Despite thorough roentgen-ray study, no cases of massive collapse were noted and there was no reference to the subject. He commented upon the fact that only a few cases were typical pneumonias, and referred to a type which showed resolving shadows within twenty-four to forty-eight hours with transient physical signs. He considered this to be due to congestion and exudation within the alveoli without fibrin and without hepatization, a type which the French named "Maladie de Woilley," but which Whipple calls a type of pneumonitis. It seems possible that some of these cases are in reality massive pulmonary collapse.

F. A. C. Scrimger,[11] of Montreal, in October, 1920, reported 7 cases of postoperative pulmonary collapse before the Clinical Congress of the American College of Surgeons. In his publication, he described fully the clinical findings in these cases, illustrating his text with numerous radiographs.

My group of cases exhibit symptoms, physical signs and roentgen-ray findings, very similar to his.

Case I.—W. C., aged twenty-nine years. Operation, February 20, 1919, for ventral hernia, subsequent to a gunshot wound of the right hypochondrium. Ether anesthesia, 10 ounces. Duration of operation, one hour and twenty-five minutes.

Case II.—W. T., aged twenty-two years. Operation, March 7, 1919, left inguinal hernia. Ether anesthesia, 6 ounces. Duration of anesthetic, thirty minutes.

This case is of particular interest in that, although the operation was a left inguinal herniorrhaphy, the pulmonary collapse was right sided.

CASE III.—W. M., aged twenty-five years. Operation, March 7, 1919, right inguinal hernia. Ether anesthesia, 8 ounces. Duration of anesthetic, one hour and twelve minutes.

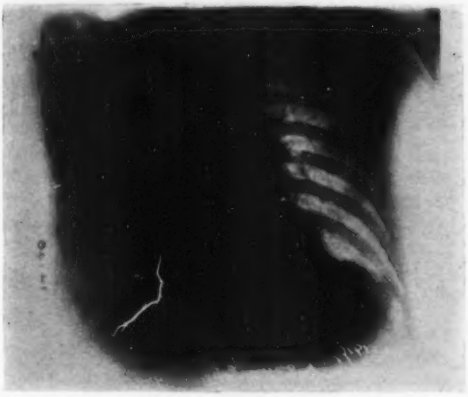

FIG. 1.—Case I, February 21. Day following operation. Diffuse dense shadow of entire right lung. No cardiac displacement.

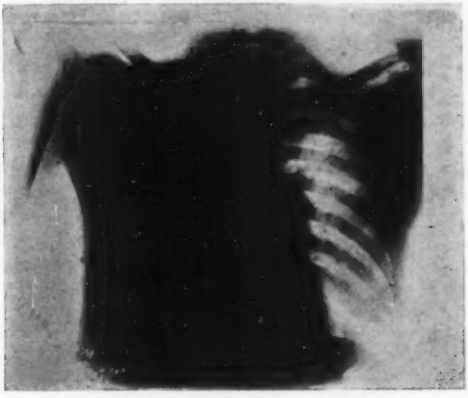

FIG. 2.—Case I, February 23. Diffuse dense shadow of entire right lung with marked cardiac displacement to the right, *toward the affected side.*

This case is of particular interest in that it is the only one described, to the best of my knowledge, which shows collapse, and recovery, alternately for six days, as corroborated by the symptoms, physical signs, and the radiographic findings.

CASE IV.—J. D., aged twenty-four years. Operation, February 25, 1919, left inguinal hernia. Ether anesthesia, 8 ounces. Duration of anesthesia, one hour.

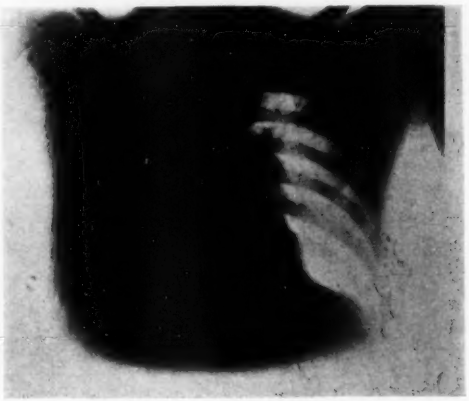

FIG. 3.—Case I, February 24. Same density of right lung, with heart shadow farther toward the left, tending to resume its normal position.

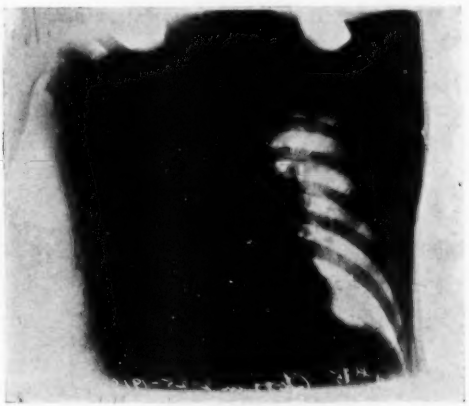

FIG. 4.—Case I, February 25. Clearing of right basal shadow with heart shadow in almost normal position. Note marked elevation of right diaphragm.

The 4 cases, which I have described, belong to the type of massive pulmonary collapse characterized by sudden onset of such severity as to suggest embolism, or acute pneumothorax. No cases of the latent type were encountered. The diagnosis of acute pneumothorax of the left side had been made in 1 of these patients (Case

I) because of the hyperresonance of the unaffected side, and the cardiac displacement toward the right.

The symptoms in these cases were of sudden onset, with marked dyspnea and cyanosis, with sharp elevation of temperature, and a disproportionately high pulse and respiratory rate.

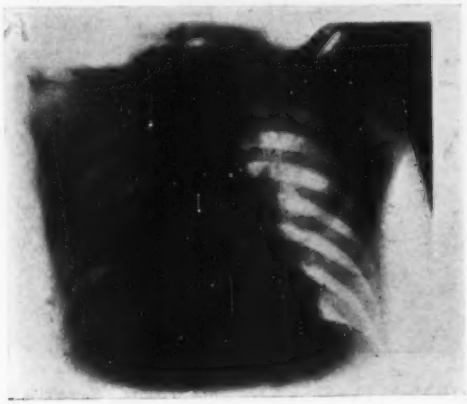

FIG. 5.—Case I, February 26. Very marked clearing of right lung, in striking contrast to roentgen-ray of previous day. Heart in normal position. There is still some elevation of right diaphragm.

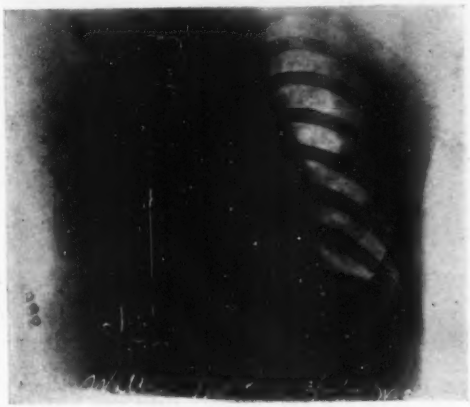

FIG. 7.—Case II, March 10. Dense shadow of entire right chest. Heart slightly displaced to the right, *toward the affected side.*

The physical signs were those of limitation of expansion of the affected side, with markedly diminished or absent breath sounds at the base, sometimes very distant tubular breathing toward the

apex. The heart was always displaced *toward* the affected side. All writers on the subject insist that this is *the* physical sign which must be present to establish the diagnosis. It absolutely differ-

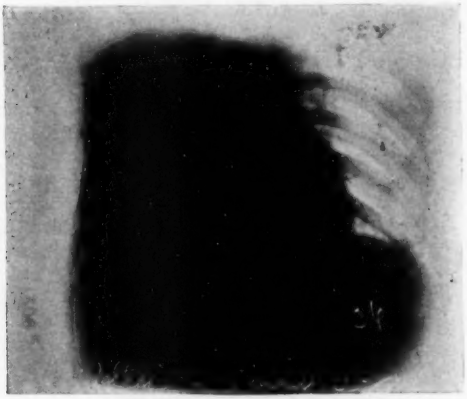

FIG. 8.—Case II, March 12. Shadow not quite so dense. Some clearing in the right lateral area. Heart shadow not so much displaced.

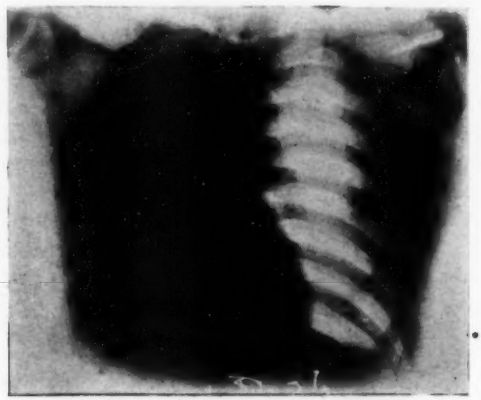

FIG. 9.—Case II, March 13. Shadow less dense, with evidence of clearing in region of the right upper lobe and laterally. Heart still displaced somewhat to the right.

entiates this condition from massive pneumonia, massive pleural effusion, and acute pneumothorax. Neither massive pneumonia nor massive effusion could possibly exhibit such remarkably sudden changes from day to day, as seen particularly in Case III, where

the pulmonary shadow appeared, and largely disappeared alternately for six days.

It is difficult to explain the sudden rise in temperature coincident with the collapse attack and the clinical chart as a whole, without

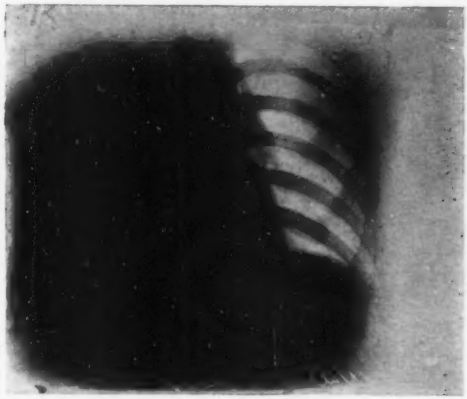

FIG. 10.—Case II. March 14. Shadow much more dense. Heart displaced a little more to the right than on previous day. A comparison with the roentgen-ray of previous day indicates a secondary collapse.

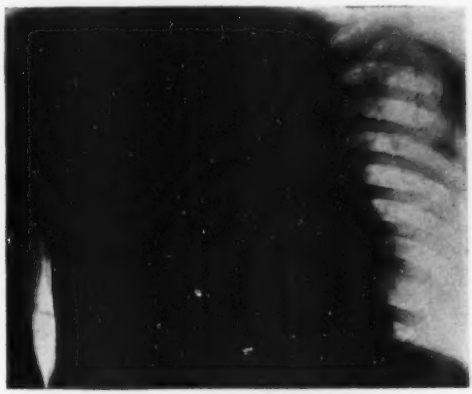

FIG. 12.—Case III. March 9. Very dense shadows of entire right chest with marked cardiac displacement *toward the affected side.*

accepting the belief that there is infection in the collapsed lung. The disproportionate rise in pulse, rate and respiration is easily accounted for on the basis of the sudden onset of the collapse with marked cardiac displacement, and severe circulatory embarrass-

ment. Case I exhibited a leukocytosis of 34,800 on the day following the collapse attack.

The first glance at the radiographs of these cases, impresses one with the absolute density of the involved lung. Not even a large

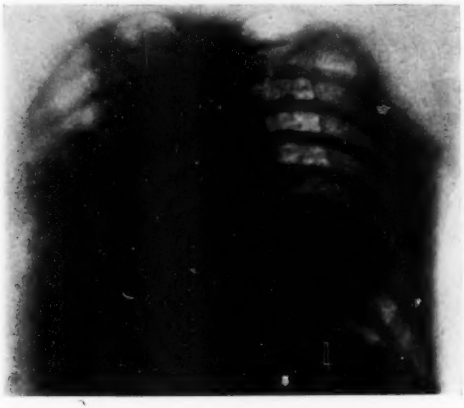

FIG. 13.—Case III, March 10. Marked evidence of clearing in area of upper lobe and laterally contrasted with roentgen-ray of previous day, with return of heart shadow to the left, almost to its normal position.

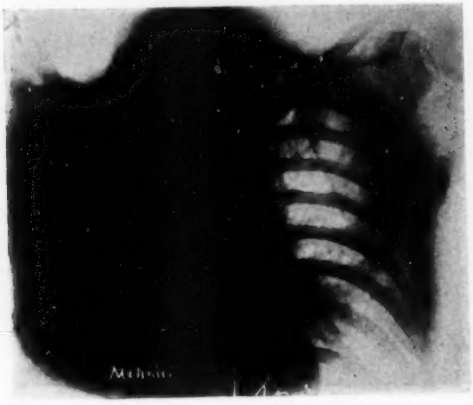

FIG. 14.—Case III, March 11. Recurrence of dense shadow of right chest, with heart greatly displaced toward the right. Very similar to Fig. 12.

empyema obscures the rib shadows so completely. It seems that there must be more than pulmonary collapse present to explain these unusual radiographs. Massive pleural effusion is eliminated as a possibility, because the cardiac displacement is toward the

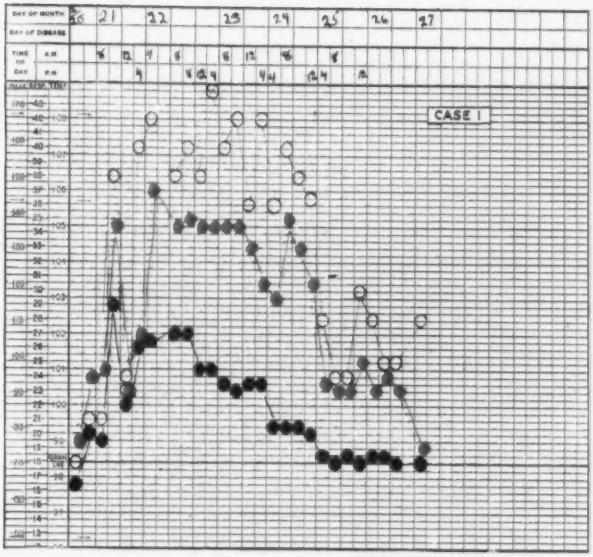

FIG. 6.—Case I, clinical chart. There was a sharp rise of temperature to 103° F., pulse 136, respiration 38, on day following operation. This was coincident with the "collapse attack." Note return of temperature to normal with sharp drop of pulse-rate and respiratory-rate on February 24, when roentgen-ray still showed marked density of entire right lung.

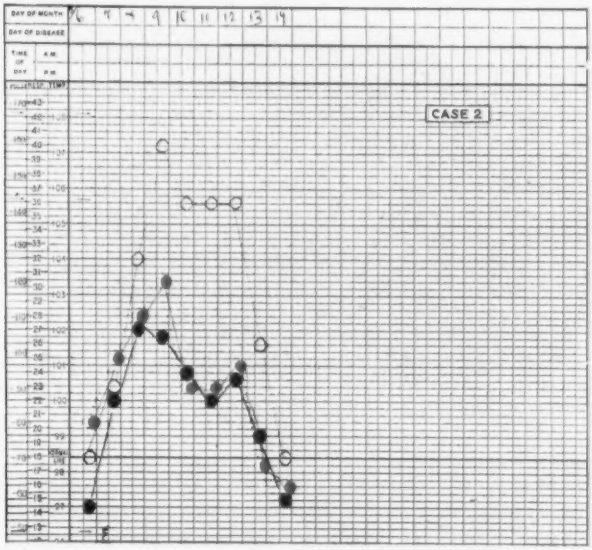

FIG. 11.—Case II, clinical chart. "Collapse attack," probably occurred March 8, the day following operation, at which time the temperature rose to 102° F., pulse 110, respiration 32. On March 14 the temperature, pulse and respiration were normal, despite the extensive lesions seen in the roentgen-ray, which shows greater density of the right lung than that of the previous day.

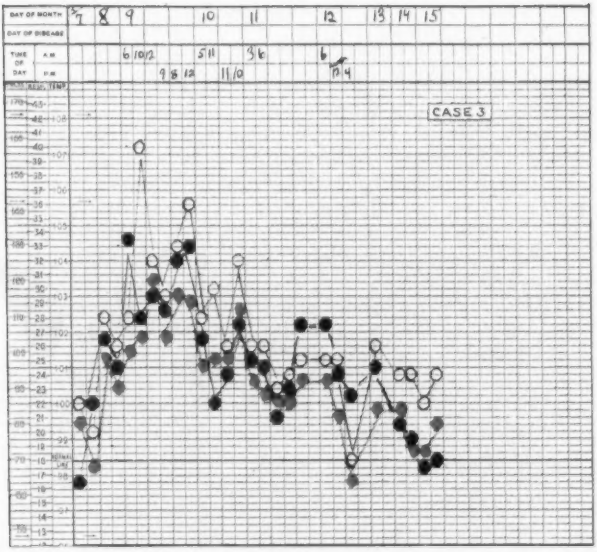

FIG. 18.—Case III, clinical chart. "Collapse attack," occurred March 8, the day following operation. It is interesting to note that the rises of temperature, pulse and respiration occurred coincidently with the times that the radiographs showed dense shadowing and that the remissions correspond to the times when the radiographs showed marked clearing of the shadow and the return of the heart toward its normal position.

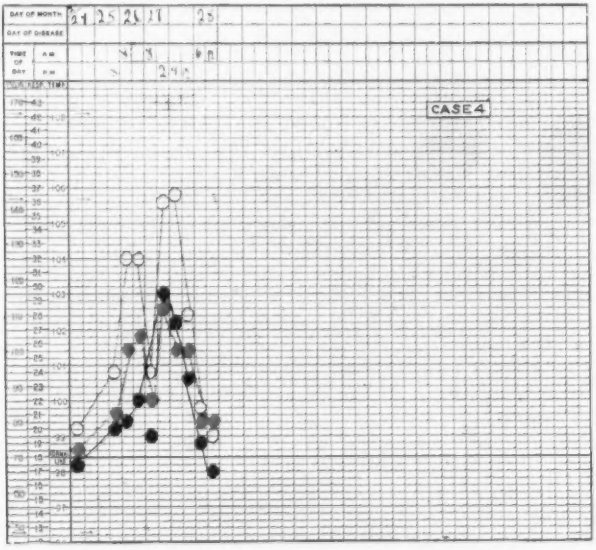

FIG. 21.—Case IV, clinical chart. Typical chart with elevation of temperature, pulse and respiration. Note that the entire duration of the postoperative complications was two days.

affected side, and is impossible, when we take into consideration comparative daily roentgen-rays. A small amount of fluid, which has no great bearing on the condition may possibly have been present. Because of the position of the heart, exploratory pleural puncture was not done.

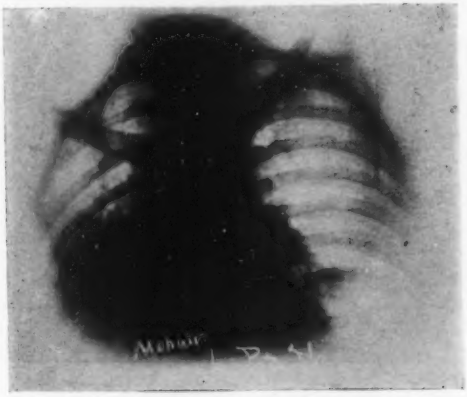

FIG. 15.—Case III, March 12. Remarkable clearing of shadow contrasted with previous day. Heart less displaced than in Fig. 14.

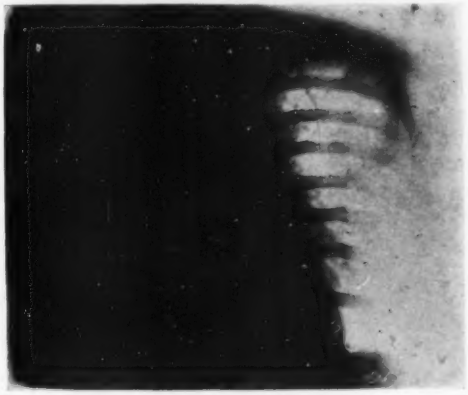

FIG. 16.—Case III, March 13. Extremely dense shadow as in Figs. 12 and 14, with similar cardiac displacement.

The most likely assumption, on which to explain the extraordinary roentgen-ray density, all things being considered, is that there is retention of secretions (fluid) within the collapsed lung.

Chevalier Jackson,[12] in the most recent edition of his book, on Bronchoscopy and Esophagoscopy, reproduces a radiograph showing the lodgment of a foreign body, the foot of an alarm clock, in the left main bronchus. The left lung is diffusely opaque and the

FIG. 17.—Case III, March 14. Marked clearly in area over upper lobe and laterally very similar to Figs. 13 and 15, with heart shadow nearly in its normal position.

FIG. 19.—Case IV, February 26. Dense shadow, lower left chest. Heart displaced toward affected side.

cardiac shadow is definitely displaced toward the left (the affected side). He describes this as "atelectasis and drowned lung," a diagnosis based on direct bronchoscopical observation.

Unfortunately, there were no facilities to do direct bronchoscopy on any of these cases, nor have I been able to find a record of it

having been done in any of the cases of postoperative collapse, but pending the appearance of the next case, which Dr. Jackson is very eager to bronchoscope, I should like to adopt Dr. Jackson's words, "drowned lung," and apply them to this condition, and consider that these cases are best described as "*postoperative massive pulmonary collapse and drowned lung.*"

Postoperative massive collapse of the lung, that which I am pleased to term massive collapse and drowned lung, has been accepted as a definite clinical entity since Pasteur's brilliant contributions, but the mechanism whereby this condition is produced has always been a subject of controversy, and so remains.

FIG. 20.—Case IV, February 27. Involved area much clearer. Heart in normal position.

Pasteur[5] believes that it is due to an active collapse, the result of some deflating force which compresses and empties the lung in the absence of any obstruction of the airway, and attributes it to paralysis of the diaphragm and intercostals. That this explanation is not tenable for all cases is certain, for many reasons. According to Briscoe[13] and others, diaphragmatic paralysis, due to phrenic nerve injury, does not reproduce this picture. Secondly, it was pointed out by Elliott and Dingley,[14] that if the condition was due to active pulmonary collapse, it would have to be assumed that the alveolar walls have active contractile power, which assumption has no support in present physiology.

If this were true, however, Elliott and Dingley maintain that the pressure on the affected side would be higher and the heart would be displaced away from the affected side. We know that this does not occur.

Lichtheim,[15] in 1878, studied the subject of pulmonary collapse by introducing into the bronchi of rabbits laminaria plugs, without

opening the thorax. As the plug swelled, the lung behind it collapsed. He found that collapse did not occur when the pulmonary vessels were tied. He, therefore, concluded that collapse occurred by the absorption of the alveolar air into the blood. From this Elliott and Dingley conclude that the bronchus becomes blocked with secretion, then the air contained in the lung is absorbed into the blood, creating, to phrase it roughly, a vacuum, which causes the diaphragm to rise and the heart to be displaced toward it. The early occurrence of viscid expectoration, as a usual symptom in these cases, suggests that the bronchus has been plugged with this secretion.

If bronchoscopical examination during a collapse attack will demonstrate complete bronchial obstruction in the bronchus supplying the collapsed and "drowned lung," then this explanation would seem correct, for those cases which occur postoperatively. It does not, however, explain all cases of massive collapse.

Sir John Rose Bradford[16] calls attention to the fact that massive collapse of the lung may occur in a variety of ways other than postoperatively. It may occur as the result of a gunshot wound of the chest wall, where no anesthetic has been given, where no penetration has occurred, and where the wound is so slight that patients are not confined to bed prior to the collapse attack. He states that massive collapse occurs in 5 to 10 per cent of all cases of gunshot wounds of the chest. It may be homolateral or contralateral, and often follows trivial injury without penetration of the pleura. It may also follow severe injuries, such as fracture of the pelvis and femur where there has been no chest injury.

If postoperative massive collapse and drowned lung has a pathology distinct and separate from that of massive pulmonary collapse occurring from other causes, then the opinion of Elliott and Dingley, that the postoperative type is due to bronchial obstruction, is probably correct. Direct bronchoscopy during a collapse attack should decide the question. No explanation has been offered to explain massive collapse occurring under the conditions which Sir John Rose Bradford describes.

It is my belief that the two conditions are dissimilar, each having a different cause. The former is probably due to bronchial obstruction with resulting atelectasis and drowned lung, the latter a simple atelectasis, without bronchial obstruction and without drowned lung. Perhaps it will be found that the latter results from some sudden vasomotor disturbance.

Summary. Four cases of postoperative massive pulmonary collapse are presented, each with comparative roentgen-rays and clinical charts.

The extreme radiographic density of the pulmonary tissue makes it necessary to consider this condition to be more than simple massive atelectasis.

The opinion is advanced that "massive collapse and drowned

lung" exist and that the radiographic findings are thus better explained.

Complete bronchial obstruction offers the best explanation for the cause of this condition, despite the fact that direct bronchoscopy during a collapse attack has not been done in any of these cases.

Pulmonary collapse occurring under conditions other than those seen postoperatively, is probably pure atelectasis, without drowned lung, and has a different cause, which may be a sudden vasomotor disturbance.

It would appear that massive collapse and drowned lung are more common than the surveys of postoperative pulmonary complications would indicate, and that the possibility of its occurrence should always be kept in mind, especially when called upon to see "postoperative pneumonia."

The recognition of these cases is of great importance, as their prognosis is vastly better than that of postoperative pneumonia, embolism, and acute pneumothorax—the conditions with which massive collapse and drowned lung are most frequently confused.

I desire to express my great indebtedness to Captain Robert Shoemaker, M.C., U. S. A., for taking the radiographs which are here reproduced; to Dr. Henry Pancoast, who, in the absence of Captain Shoemaker, interpreted them for me, and to Dr. Chevalier Jackson for his kindly criticism and advice.

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A CASE OF PRIMARY CARCINOMA OF THE BLADDER WITH METASTASIS TO THE BRAIN.

By William E. Lower, M.D.,
and
Ralph M. Watkins, M.D.,
Cleveland Clinic, Cleveland, Ohio.

In a careful search of the literature we have not been able to find that any case in which a metastasis in the brain has developed from a primary carcinoma in the bladder has ever been reported. Therefore an encounter with a case in which the tissue from a growth in the brain was of the same nature as that of an original growth in the bladder makes it seem worth while to publish this report.

Case Report. The patient, a male, white, aged forty-eight years, entered the Cleveland Clinic on April 19, 1922. Except for the death of an older sister from tuberculosis his family history was negative. He had been married eight years and had one child. His past health had been fairly good. He had had pneumonia at the age of six years, scarlatina at ten, a small hernia and varicocele (never operated upon) while in college; and during the immediately preceding years, several attacks of tonsillitis. His habits were fairly good: a moderate use of alcohol, but no tobacco and no coffee.

The patient reported at the Clinic because of difficulty in urinating. Ten months before this, life insurance had been granted him in spite of the presence at the time of some bladder irritation; but three months after that examination he had failed to pass another examination for insurance because of the presence of blood and albumin in the urine. A physician prescribed a special diet and asked him to report again in a month. He had not improved, and his tonsils and a nasal growth were held to account for his condition. About April 1, he had a sharp attack of hematuria following horseback riding. A cystoscopical examination by Dr. Louis E. Schmidt of Chicago, disclosed a bladder tumor, probably malignant. When he came to the Clinic he was having some difficulty in emptying the bladder, and showed also a little loss of control of his left foot and a slight speech defect.

Physical Examination. The patient was a well-nourished man, weight 185 pounds, height 5 feet 10 inches. The skin was a trifle pale, but showed no rashes; pupils equal, regular, reacted well to light, no ocular palsy; glasses worn for myopia; teeth showed a great deal of dental work but were in good condition; pharynx red; tonsils chronically inflamed; tongue slightly coated; nasal septum was markedly deflected by old trauma; no thyroid nor glandular enlargement; lungs normal; heart, aorta, and palpable arteries normal; pulse rate 70; blood-pressure 140–95; no tenderness nor

masses in abdomen, and no palpable enlargement of organs; small left inguinal hernia; extremities negative; reflexes equal and active. Roentgen-ray examinations of the skull and pelvis were negative.

A cystoscopical examination revealed a round fungating tumor just inside the internal sphincter slightly to the right of the median

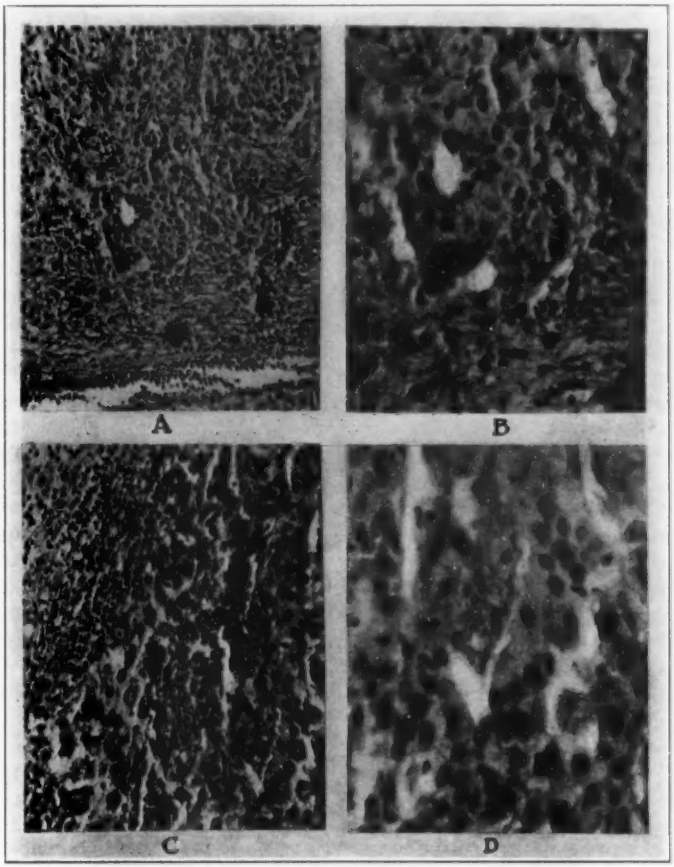

FIG. 1.—*A*, carcinoma of the bladder (low ×); *B*, carcinoma of the bladder (high ×); *C*, metastasis to the brain (low ×); *D*, metastasis to the brain (high ×).

line; the whole tumor could not be seen in one field of the instrument. The urine showed 30 to 50 erythrocytes per field, and a great many pus cells; the blood count showed 5,020,000 red cells, 7200 white cells, and 75 per cent hemoglobin. The phenolsulphonephthalein test showed a total elimination of 45 per cent—

25 per cent the first hour and 20 per cent the second hour. The blood Wassermann test was negative.

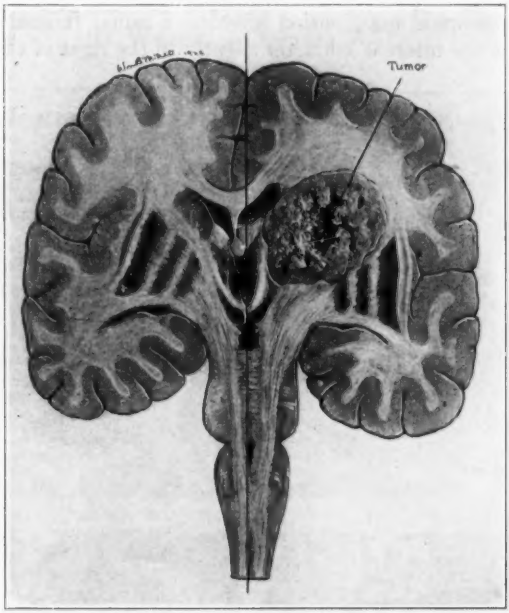

FIG. 2.—Schema, showing position of brain metastasis.

FIG. 3.—Brain metastasis.

The possibility that there might be also a tumor of the brain was considered at this time, but since the eye-ground examination and the roentgen-ray examination of the skull were negative, this opinion was not supported.

On April 24, the growth in the bladder was removed by a suprapubic incision. Because of the apparent malignancy, 65 mg. of radium were applied for six hours at the seat of the tumor. Healing was uninterrupted.

Gross Pathology of Bladder Tumor. The tumor was 1½ cm. in diameter, rounded, firm, with a fairly small pedunculated base surrounded by a section of the bladder wall.

Histo-pathology of Bladder Tumor. The sections show a rather loose connective-tissue stroma largely invaded by malignant transitional epithelial cells. There is a tendency for the masses of tumor cells to form alveoli. These tumor cells are arranged around a connective-tissue base as if pedunculated and in this connective tissue are epithelial lined spaces which are either dilated ducts or acini which are benign (Fig. 1, A and B).

Pathological Diagnosis: Transitional-cell carcinoma of the urinary bladder.

A short time after the removal of the bladder tumor the difficulty in walking and the speech defect became more pronounced and a clinical diagnosis of brain tumor was made.

On June 6, 1922, six weeks after the bladder operation, Dr. Walter E. Dandy, of Baltimore, removed from the right internal capsule, a circumscribed tumor which he believed to be a metastatic carcinoma (Fig. 2). The patient made an excellent recovery from the operation.

Gross Pathology of the Metastatic Tumor. The tumor was rather firm in consistency and about 2 cm. in diameter. It was generally spherical in shape, with a rather irregular surface. The color was light gray; there was little gross increased vascularity. It cut like a very cellular tumor and on section, seemed to be entirely encapsulated. The central tissue was soft, friable, and apparently somewhat degenerated. It had many small papillary projections (Fig. 3).

Histo-pathology of Metastatic Tumor. The sections show essentially the same picture as those presented by the bladder tumor. The epithelial cells are malignant, are of the transitional type, and like those of the primary tumor have a tendency to group themselves in alveoli. The stroma consists of neuroglia tissue.

Pathological Diagnosis of Metastatic Tumor: Transitional-celled carcinoma of the brain, metastatic from carcinoma of the bladder.

On November 8, 1922, seven months after the removal of the bladder tumor a cystoscopical examination disclosed a suspicious area in the region of previous growth. Another examination on February 12, 1923, ten months after the operation, showed that the bladder was free from any signs of recurrence. At this time there was still some paralysis of the left arm and leg and the difficulty in speech had increased. The patient died early in April, 1923, ten months after the removal of the brain tumor, the cause of death being a recurrence of the brain metastasis.

REVIEWS.

A Manual of the Practice of Medicine. By A. A. Stevens, A.M., M.D., Professor of Applied Therapeutics in the University of Pennsylvania; Visiting Physician to the Philadelphia General Hospital. Prepared especially for students. Eleventh edition, entirely reset. Pp. 645; 16 illustrations. Philadelphia and London: W. B. Saunders Company, 1923.

Although too brief and sketchy in character for the routine use of the modern fourth year medical student it would seem that this manual, which is certainly the standard one in English, is ideally suited for the first and second years, especially since an effort is now being made to introduce the clinical subjects in outline at that time. It also has a value in that it affords older students and physicians a means of rapidly reviewing the entire subject of medicine. The reviewer has found it of signal help also in the instruction of nurses. Its accuracy is guaranteed by Dr. Stevens' experience as a teacher and practitioner and by the eleven editions within thirty-one years. M.

Heliotherapy. By A. Rollier, M.D., Medical Director of the Institutions for Heliotherapy, Leysin; Laureate of the Academy of Medicine, Paris; Correspondent Member of Societies of Medicine and Pediatrics, Paris. With the Collaboration of A. Rosselet, D.Sc., Lecturer on Physicotherapy, Geneva University; formerly Assistant at Rollier's Institutions, Leysin. H. J. Schmid, M.D., Radiologist at Rollier's Institutions, Leysin; and E. Amstad, M.D., Surgeon at Rollier's Institution, Leysin. With Forwards by Sir John Henry Gauvain, M.A., M.D., M.R.C.S., L.R.C.P., and Caleb William Saleeby, M.D., F.R.C.S. Pp. 288; 52 illustrations. London; Henry Frowde, Hodder & Stoughton (Oxford Medical Publications), 1923.

Heliotherapy, because of its recent resurrection from great antiquity is considered a modern therapeutic agent. Dr. Rollier's enthusiasm is infectious. He clearly states the indications and contraindications to heliotherapy and considers it a curative agent in surgical tuberculosis (bone and joints), but he goes a bit beyond

his scope when he sights a case of diabetes mellitus, in which glycosuria was controlled by exposure to sunlight. One hundred and eight pages are devoted to case reports that were cured at the author's institutions, which seem much like testimonials. No mention is made of failures. The chapters on the "Scientific Basis of Heliotherapy," the "Radiological Diagnosis of Osteoarticular Tuberculosis and the Radiographic Control of the Clinical Results of Heliotherapy" and "The Adjuvants of Heliotherapy" are well written. The book has a distinct niche in medical literature as a stepping stone to a more exhaustive treatise of a subject not yet fully appreciated. L.

PRINCIPALS AND PRACTICE OF INFANT FEEDING. By JULIUS HESS. Third edition. Pp. 496; 34 illustrations. Philadelphia: F. A. Davis Company, 1923.

IN the third edition of his already well-known manual on infant feeding, Hess has enlarged upon the commonly met symptoms in infancy. He has also added chapters dealing with the diseases of metabolism.

The book is concise, complete and most handy for ready reference for teacher, student or practitioner. It is well illustrated by nicely selected clinical cases and records.

This book deserves a readily accessible space among text-books. D.

MENTAL DEFICIENCY (AMENTIA). By A. F. TREDGOLD, M.D., M.R.C.P., F.R.S., (EDIN.), Lecturer on Mental Deficiency at the London University. Fourth edition. Pp. 569; 30 illustrations. New York: William Wood & Co., 1922.

THIS is the fourth edition of this well-known work and it consists of twenty-two chapters with an appendix and index, eighteen tables and thirty illustrations.

The first three chapters are largely introductory. The next four chapters are given to a discussion of pathology, classification, neurophysiology and psychology and the physical characteristics of amentia. The remainder of the book takes up various forms of amentia, its diagnosis and prognosis and the various forms of treatment.

The illustrations are excellent but the type is rather small. From a scientific point of view Tredgold has written an excellent book in which mental deficiency is discussed from every angle. The style is easy and the book should be in the library of every up-to-date physician. W.

LOCAL ANESTHESIA METHODS AND RESULTS IN ABDOMINAL SURGERY. By PROF. DR. HANS FINSTERER, Surgeon-in-Chief, Vienna Hospital of the Brothers of Charity. Authorized English version by JOSEPH P. F. BURKE, M.D., Sc.D., LL.D., Attending Surgeon, Buffalo Hospital of the Sisters of Charity. Pp. 331; 42 illustrations. New York: Rebman Company, 1923.

THE markedly successful results with various forms of local and conductive anesthesia in the hands of the author are presented to the English reader in an excellent translation by his pupil, the translator. The first part of the book discusses the general considerations, the indications and technic of the various forms of conductive anesthesia. The second part of the book deals with the application of these methods in abdominal surgery, gynecology and urology. Many case histories are used in detailing the different modes of procedure. The book closes with a full and up-to-date bibliography, with an unusually large number of American references. W.

MISTAKES AND ACCIDENTS OF SURGERY. By HAROLD BURROWS, C.B.E., M.B., B.S. (LOND.), F.R.C.S., Assistant Surgeon with the British Expeditionary Force in France; Late Hunterian Professor of Surgery at the Royal College of Surgeons of England. Pp. 470. New York: William Wood & Co., 1923.

THERE is a wealth of clinical wisdom in the pages of this little book. It is not a resultory account of interesting or amusing errors of omission or commission. The author systematically reviews the whole subject of regional surgery with reference to the chief pitfalls of judgment and technic. Such a book is born of long experience only. The embryo surgeon would do well to read and consider; the more mature will be diverted and fortified in many conclusions gained from his masters or learned in a harder school. P.

FUNCTIONAL AND NERVOUS DISORDERS. Their Classification and Treatment. By DONALD E. CORE, M.D., Lecturer in Neurology, University of Manchester, England. Pp. 371; 21 illustrations. New York: William Wood & Co.

THIS book is divided into six parts; taking up in order general considerations, the regressive group of the functional nervous disorders, the progressive or sympathetic nervous disorders, some considerations regarding the functional nervous disorders in general, diagnosis and prognosis, and lastly treatment. In this work on

functional nervous disorders Core has given to the profession an excellent book on the diagnosis and treatment of the psychoneuroses. The chapters on treatment are full of excellent ideas for the handling of a very difficult group of cases. Core recognizes, as most neuropsychiatrists do, that the sex instinct can bring about a neurosis, but that it is not responsible for the vast majority of functional nervous disorders. One might express surprise that the epoch making writings of Babinski in regard to hysteria are not more frequently mentioned. W.

INTRODUCTION TO MEDICAL BIOMETRY AND STATISTICS. By RAYMOND PEARL, Professor of Biometry and Vital Statistics in the School of Hygiene and Public Health and of Biology in the Medical School, Johns Hopkins University. Pp. 379; 71 illustrations. Philadelphia and London: W. B. Saunders Company, 1923.

THIS book will appeal primarily to the medical writer and research worker desiring to know how best to obtain and handle his statistical data. The physician who is puzzled by such terms as "skewness," "coefficient of correlation," "probable error," etc., which appear with even increasing frequency in the medical literature of the day, will likewise find this work enlightening, but difficult to understand unless he be gifted to an unusual degree with talent for mathematics. On the other hand, the expert mathematician will perhaps be disappointed in failing to find the detailed approach and the mathematical proof of many of the formulæ appearing in these pages. A.

BLUTKRANKHEITEN UND BLUTDIAGNOSTIK. By O. NAEGELI, M.D. O. Ö. Professor der inneren Medizin an der Universität Zürich und Direktor der medizinischen Universitätsklinik. Fourth edition. Pp. 587; 62 illustrations. Berlin: Julius Springer, 1923.

THIS book is one of the standard books on the morphology of the blood cells, dealing with the pathological state of the blood and bone-marrow as well as the norm. Dr. Naegeli discusses in full and with minute detail, diseases that are associated with disturbances of the red cells, the white cells and infectious diseases. There is no mention, however, of the chemistry of the blood. This is not an oversight nor is it a fault to be criticised because the book is in no sense meant to be a complete treatise on the blood, which of course would include chemistry of the blood. It is, as the title says, merely a treatise on blood diseases and blood diagnosis, meaning the blood cells themselves. The work is the best piece of the

printer's art that we have seen from Germany since the war, the paper is of good quality, there is an absence of typographical errors and the numerous colored plates at the end of the book are beautifully executed. M.

LABORATORY DIAGNOSIS OF SYPHILIS. By HIDEYO NOGUCHI, M.D., M.S., PH.D., D.SC., Member of the Rockefeller Institute for Medical Research, New York, Pp. 392; 59 illustrations, of which 13 are in color. New York: Paul B. Hoeber, 1923.

THIS book aims to present the elementary principles of hemolysis and complement-fixation as applied in the serum diagnosis of syphilis, and also details methods for the identification of Treponema pallidum.

Emphasis is very opportunely placed upon the advantages of dark-ground illumination over staining methods for the identification of treponema. The principles and the technic of dark-field microscopy are very well presented. Among the staining methods, the simplified and reliable buffered-formalin method from the author's laboratory is described. Cultural methods for the Treponema pallidum and animal inoculations procedures for their detection are omitted.

The Wassermann reaction is presented in much the same manner as in the author's *Serum Diagnosis of Syphilis*, 3d ed., 1912, with all its inherent objectionable features passed over lightly. The practical difficulty of preparing antihuman amboceptor is mentioned, but no mention is made of the difficulties arising from the appearance of specific hemoagglutinins in such antisera. While attributing the lack of standardization of the Wassermann reaction to unknown and variable quantities of amboceptor inherent in the hetero-hemolytic systems, the author yet recommends the inaccurately gauged doses of available amboceptor used in the homo-hemolytic system in the form of serum dried on paper. In the chapter presenting the system of serum diagnosis recommended by the author no mention is made of the titration of complement.

In discussing the effects of treatment upon the Wassermann reaction, much of the material upon which the argument is based is represented by work done prior to 1912, so that statements of 1250 cases treated with salvarsan with 40 relapses; 110 cases with 3 relapses; 789 cases with 33 relapses, appear as obsolete and worthless data in the light of present-day syphilology.

The luetin reaction is presented as favorably as possible by omitting the recent more critical inquiries into its value.

An extensive bibliography is appended, but here again, so far as serology is concerned, the greater number of the references are old and chiefly of historical interest. S.

PHYSICAL DIAGNOSIS. By W. D. ROSE, M.D., Lecturer on Physical Diagnosis and Associate Professor of Medicine in the University of Arkansas. Third edition. Pp. 755; 319 illustrations. St. Louis: C. V. Mosby Company, 1922.

DR. ROSE'S book takes up first the physical examination of the thorax and respiratory organs with a very thorough consideration of percussion signs and breath sounds. The various diseases of the respiratory organs are then discussed fully. The examination of the heart is treated in a thorough manner and this section has been revised so that it includes important recent work in cardiology. The discussion of heart murmurs is exceptionally good. There is a chapter on the Diagnosis of Abnormalities of the Heart Beat, by Dr. Drew Luten. Examination of the abdomen and abdominal organs and examination of the kidneys are fully discussed and examination of the nervous system briefly treated.

This book is well written, the subject matter well divided and the illustrations numerous and well chosen. The treatment of physical signs in diseases of the lungs are especially good. This is an excellent text-book on physical diagnosis. T.

THE FORM AND FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM. AN INTRODUCTION TO THE STUDY OF NERVOUS DISEASES. By FREDERICK TILNEY, M.D., PH.D., Professor of Neurology, Columbia University, and HENRY ALSOP RILEY, A.M., M.D., Associate in Neurology, Columbia University, with a foreword by GEORGE S. HUNTINGDON, Sc.D., M.D., Professor of Anatomy, Columbia University. Second edition. Pp. 1019; 763 illustrations. New York: Paul B. Hoeber, 1923.

THE intention of the authors of this book to incorporate the anatomy and physiology of the central nervous system as essential parts of the practical knowledge necessary to the proper diagnosis and treatment of disease has been so well accomplished that this second edition has been demanded. The work has successfully brought about the result for which it was designed, namely, "To fill the gap between morphology and the practical requirements of clinical medicine; to visualize the living nervous system, to make accessible an appreciation of its vital relation to the functions; which go to make up life, as well as the defects in these relations which result in disease."

The great value of the book to every medical student, more particularly perhaps to the one who intends to take up neurology as a specialty, as noted on the appearance of the first edition, is again here stressed. O.

AN INTRODUCTION TO THE STUDY OF MENTAL DISORDERS. By FRANCIS M. BARNES, JR., M.A., M.D., Associate Professor of Nervous and Mental Diseases in the St. Louis University Medical School. Second edition. Pp. 295. St. Louis: C. V. Mosby Company, 1923.

THIS book is a combination of two of Dr. Barnes' former works, namely, his *Introduction to the Study of Mental Diseases* and his *Notes on Mental Diseases*, which have been revised and considerably amplified, with some entirely new chapters added, and more extended consideration given to certain types of mental disease. The new chapters have to do with the subject of mental hygiene and social psychiatry, also the mental factor in industry and vocational guidance. They are both well written, and the sound interpretation of mental hygiene very well stresses the present method of study of mental medicine, *i. e.*, the progressive mind of the psychological conception. This is well balanced by the importance paid to the non-specificity of mental disease in another chapter. The book can be heartily recommended to medical students as a brief of psychiatric fundamentals, which will be of great value to psychiatric social workers as well. G.

MINOR MALADIES. By LEONARD WILLIAMS, M.D., Physician to the French Hospital. Fifth edition. Pp. 414. New York: William Wood & Co., 1923.

THIS little book will always prove useful because the minor maladies are often the most difficult things the physician has to treat. It is full of practical suggestions and has a certain ease of presentation which is so characteristic of English medical writings. M.

THE CARE OF THE BABY. By J. P. CROZER GRIFFITH, M.D., Professor of Pediatrics in the University of Pennsylvania: Physician to the Children's Hospital and Consulting Physician to St. Christopher's Hospital for Children. Seventh edition. Pp. 478; 104 illustrations. Philadelphia: W. B. Saunders Company, 1924.

GRIFFITH'S book on the care of the baby has been a standard since 1895. The fact that it has reached such an enormous circulation and is so extensively used is sufficient evidence of its value. M.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

Isoagglutination in New-born Infants and Their Mothers. A Possible Relationship Between Isoagglutination and the Toxemia of Pregnancy.—In an interesting study of the isoagglutination reaction in 180 women and their new-born infants, McQUARRIE (*Bull. Johns Hopkins Hosp.*, 1923, **34**, 31) finds the blood group to be completely established at birth in 11 per cent of the infants and to be partially established in over half. The blood group of the infant might or might not be the same as that of the mother, so that McQuarrie concludes the intact placenta is impermeable to isoagglutination. Sixteen outspoken cases of eclampsia and 24 of mild or potential eclampsia were included in the study, and it is most interesting to note that over 70 per cent of these cases of toxemia occurred in the small group in which there was interagglutination between fetal and maternal blood. Toxemia occurred 165 times more frequently when the maternal and fetal bloods were demonstrated to be incompatible than when they were in the same isoagglutination group. Conclusions as to the actual importance of these findings in discovering the cause of eclampsia are withheld until further work can demonstrate some mechanism by which the fetal blood can gain access to the maternal circulation. Perhaps hardest of all to be explained will be the eclamptic seizures coming on some time after delivery. A note of warning is sounded against transfusing an infant with any blood, even its mother's, without first carefully matching for agglutination.

Studies on the Influence of Pregnancy in Syphilis. 1. The Course of Syphilitic Infection in Pregnant Women.—A clinical and laboratory study was made by MOORE (*Bull. Johns Hopkins Hosp.*, 1923, **34**, 89)

of 178 pregnant women with positive blood Wassermann reactions and 22 non-pregnant mothers of syphilitic children. Pregnancy seemed to cause striking deviations from the usual course of the syphilitic infection. The early manifestations of syphilis may fail to appear if infection and impregnation appear, or if they do appear, they are much milder than is usual in non-pregnant women. This protection against the disease afforded by pregnancy often persists for many years, and in a few cases for the remainder of the patient's life. In the women who developed late manifestations of syphilis, the visceral involvement, especially cardiovascular, was most often seen. Tertiary lesion of the bones, skin and nervous system were rare. The Wassermann reaction in these cases of latent syphilis was very prone to marked vacillation without treatment, either a negative or positive reaction during pregnancy being changed to the opposite after delivery.

Bronchial Moniliosis.—STEINFELT (*Jour. Am. Med. Assn.*, 1924, **72**, 83) describes 15 patients with bronchial asthma and chronic bronchitis in whom an allergic state with regard to the usual pollen and epidermal food proteins was not demonstrable, all of whom showed an interesting bronchomycosis with the appearance of monilia in the sputa. All of these patients showed eosinophilia. The ages varied from twenty-five to sixty years. Seven were in men; 8 were in women. In all the process began in Philadelphia. Clinically these were chracteristic instances of bronchial asthma associated with general bronchitis and paroxysms of expiratory dyspnea with audible wheezing, and, in the active stages, sonorous and sibilant rales generally on both sides. In some there were also subcrepitant rales and a picture which, at times, suggested bronchiectases or tuberculous changes. But there was never dulness on percussion and all cases cleared up under proper treatment. In all of these cases there were found in the sputa, white, chalk-like particles or indeed actual islands composed of colonies of yeasts. Sometimes they were amber colored. Under the high-power objective they consisted of globular fat-like spores and sometimes in severe cases, developed hyphæ and mycelia. Cultures of these particles yielded yeasts of the genera Monilia cryptococcus and endomyces. Suspensions of cultures injected into guinea-pigs intraperitoneally or intratracheally produced eosinophilia in the exudates and in the blood, and eosinophilia were always present in the human beings. While insisting upon the careful attention to any abnormalities in nasal passages, tonsils and sinuses, it is the author's belief that striking benefit resulted from the employment of iodides in doses of from 2 to 4 gm. per day (gr. xxx to cxx). Moreover he feels that improvement was facilitated by the injection of vaccines prepared according to the method of Michel.

Hyperglycemia as an Etiological Factor in Certain Dermatoses.—MCGLASSON (*Arch. Dermat. and Syph.*, 1923, **8**, 665) has studied a large number of chronic dermatoses from the standpoint of the sugar content of the blood. Most of the conditions could be grouped under the head-

ing of "eczema," using this term generically. In but few of the cases was there a glycosuria, but most showed a blood sugar content of higher than 0.11 per cent, which was taken as the upper limit of normal. The usual treatment was used, including roentgen-ray, but in addition a restricted carbohydrate diet. The improvement was so much more striking when carbohydrate was restricted that the author concluded that a hyperglycemia was at least one of the factors in this class of dermatoses. This conclusion was strengthened by the fact that there would often be a return of the dermatitis if carbohydrate was added too rapidly to the diet. A number of extremely interesting cases are cited.

Treatment of Neurosyphilis.—SOLOMON (*Jour. Am. Med. Assn.*, 1923, **81**, 1743) describes the anatomy of the central nervous system in relation to syphilitic infection and makes a worth-while differentiation between parenchymatous syphilis, such as paresis or tabes, and meningo-vascular syphilis. He points out how the central nervous system is separated and shut off to a large extent from substances in the general circulation. In general, it was found that meningo-vascular syphilis reacts the more favorably to treatment, and this confirms previous work. Some cases of what were apparently paresis, however, did very well on the ordinary treatment with arsphenamine, mercury, and iodides. The author advocates introducing the medicament as near the site of pathological change as possible, using the lumbar, cisternal, or ventricular routes, as indicated. The immunity of the patient is a factor, and mention is made of the theory of increasing the immunity by inducing febrile reactions, such as by injection of foreign protein, or by inoculation with malaria. Solomon mentions tryparsamide in passing. Further reports of the use of this drug in paresis will be interesting.

On Bronchial Breathing.—MARTINI and MUELLER (*Deutsch. Arch. f. klin. Med.*, 1923, **143**, 129) making a new contribution to the interesting series of studies on physical diagnosis which have come from the latter's clinic. By ingenuous methods of analysis of the vibrations induced in the air content of various systems of tubes analogous to bronchi and in bronchi in the human body they come to the conclusion that the point of origin of the sonorous vibrations characteristic of bronchial breathing lies in tubes of a relatively large lumen—those with a diameter of from 4 mm. upward. To convey these sounds to the periphery so that they may be audible on auscultation of the chest there must be a continuous area of solidified tissue reaching from the periphery to a depth of from 3 to 5 cm., for such is the usual distance of such bronchi from the periphery. But a small layer of normal lung tissue masks tubular respiration. Only near the spine, in the interscapular space may areas of solid tissue from 1 to 2 cm. deep suffice to convey bronchial respiration to the ear. The conception that bronchial respiration is characteristic of solidified lung tissue and is produced in the finest bronchi with firm walls has no foundation.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Retroperitoneal Perirenal Lipoma.—JOHNSON (*Boston Med. and Surg. Jour.*, 1923, **189**, 907) says that lipomata are probably the most frequent growths in retroperitoneal sites. Owing to slow growth and lack of characteristic symptoms they attain great size before their discovery. The most common sites are the perirenal fat and the fat at the root of the mesentery. These growths are more frequent in females than in males, and between the ages of forty and fifty years. They may be pure lipomata, but rather more than half are of the mixed variety. They may undergo sarcomatous degeneration. Emaciation at times becomes marked—the condition being inoperable in some cases. Mortality is between 15 and 20 per cent.

Subperiosteal Resection of Long Bones in Osteomyelitis.—BEYE (*Surg., Gynec. and Obst.*, 1923, **37**, 732) states that it is fundamentally unsound to do a subperiosteal resection of the shaft of a long bone for osteomyelitis. In performing such an operation bone may be sacrificed, which if properly drained would not only be viable but play an important part in the restitution of the diseased shaft. Regeneration of bone from the periosteum remaining after subperiosteal resection may be limited and stop far short of a functional end-result. Deformities are likely to follow such an operation with resultant functional disability. The radical removal of diseased bone by this procedure does not necessarily mean that infection has been eliminated.

Arthoplasty.—GROVES (*Brit. Jour. Surg.*, 1923, **11**, 234) says that arthroplasty should be defined as an operative procedure upon an ankylosed joint, which has the object of restoring mobility. The pseudoarthrosis which sometimes results from a simple fracture proves that a new joint can be formed including fitting articular ends, capsule and synovia, without any plastic operation. Clinical evidence as to the result of arthroplasty is conflicting. There is ample evidence that operative mobilization of the elbow-joint is usually followed by greatly improved function, while arthoplasties for hip and knee often lead to disappointment or failure. The condition most favorable for arthroplasty is bony ankylosis due to trauma or pyemia which has long been cured. Certain cases of tubercle and osteoarthritis also give good results. The essential act in arthroplasty is to make a gap between the articular ends and to maintain this gap while healing takes place. Shaping and covering the articular ends is useful, but not essential. Continuous traction on the articulation and early voluntary movements

are the essentials of after-treatment. In the elbow the indications include all cases of bony ankylosis free from active infection, except those in which a strong useful arm is present in a laboring man. The best operation for the elbow is to preserve the whole width of the humeral condyles and to cover this bone with a free flap of fascia lata. In the hip, for simple ankylosis, an osteotomy of the neck of the femur with interposition of a flap taken from the trochanter or from the capsule. For massive hypertrophic ankylosis a subtrochanteric osteotomy, with the interposition of a fascial flap, forming a saddle-shaped joint. For osteoarthritis, excision of the head of the femur is indicated. In the knee, the importance of stability and painlessness makes any mobilizing operation unjustifiable if the joint is fixed in a good position. It is only in the cases of ankylosis of both knees that arthroplasty is to be considered. The use of free fascia to cover the lower end of the femur, the preservation of the lateral ligaments and the use of a jointed knee cage for some months after operation are the special points on which stress must be laid. If lateral mobility persists, then lateral and crucial ligaments must be reinforced by a second operation.

Bilharziasis of the Ureter.—Brahim (*Lancet*, 1923, **205**, 1184) says that bilharziasis of the ureter exists, and may be the only or the most prominent manifestation of the disease, which is usually bilateral, though more advanced on one side than on the other. The disease is very chronic and the stages merge one into the other. The disease ends in the formation of fibrous tissue which replaces the normal coats of the ureter. This leads to contractions and narrowing or even complete obliteration of the lumen of the lower part of the ureter. Secondary to this, the upper part of the ureter and pelvis of the kidney become dilated. Ascending infection is rare and is mostly a complication of bilharziasis of the bladder. If neglected, the disease is very fatal, ending in death from uremia and rarely from septicemia.

Experimental Cord Crushes.—McVeigh (*Arch. Surg.*, 1923, **7**, 573) states that edema and hemorrhage are factors to be dealt with in partial lesions of the cord. Release of pressure seems to have no effect in checking edema formation. In complete lesions of the cord, the cord at the site of the lesion is reduced to a pulp and blood mixture, and the ends of the cord separate for a short interval. The pulp is forced into segments above and below the lesion, and causes an increased intrapial pressure, which is released in one of two ways; by rupture of pia, or the tracking of pulp up and down the cord until pressure is relieved. The area of the cord involved in complete lesions is the area of least resistance, located in the ventral part of the dorsal white columns and that part of the central gray matter dorsal to the cerebral canal.

Cardiorrhaphy in Acute Injuries.—Smith (*Ann. Surg.*, 1923, **78**, 696) says that cardiorrhaphy is a comparatively recent advance in surgery. The human heart is very tolerant of manipulation. This fact has been repeatedly demonstrated, especially in connection with foreign body extractions during and since the World War. Surgical pneumothorax is remarkably well tolerated. The symptomatology of heart injuries varies widely and as a consequence the diagnosis of this

condition is often very difficult. Therefore exploratory operations are justifiable. Transpleural thoracotomy under general anesthesia is probably the procedure best suited to the average case of this type. Drainage in this case can be accomplished best through the medium of a simple valve-tube drain through the chest wall.

Surgery of Seminal Vesicles.—MORRISEY and SMITH (*Surg., Gynec. and Obst.*, 1922, **37**, 480) says that inflammation of the seminal vesicles is a well-defined and recognized surgical condition occurring usually as a sequel to previous infections of the genito-urinary tract. It is a condition that can be relieved surgically either by drainage or extirpation of the vesicles. Operation on the vesicles combine all difficulties of perineal prostatic surgery and a well-established technic must be employed properly to meet indications for operation. Procedures aiming to drain vesicles through skin incisions and punctures are ineffective, and results reported following inaccurate technic cannot be taken into account. Figures and results in a large series of cases with bacteriological findings and improvement noted in a large proportion of cases justify the establishment of the operation and a more frequent use as a surgical procedure in selected cases.

Tuberculous Enterocolitis.—LEMON (*Minn. Med.*, 1923, **6**, 572) says that the fundamental functions of the body in tuberculosis are apparently affected by the disease itself, and not influenced particularly by the site or area involved. Obstruction or stenosis and perforation are more common in tuberculous enterocolitis than has been believed. There are no characteristic symptoms which will definitely locate in any special area of the bowel. The surgical and necropsy evidence of tuberculous enterocolitis is almost invariably more widespread than the clinician could anticipate.

The Relation of the Bowel to B. Coli Kidney Infections.—DAVID and MCGILL (*Jour. Urol.*, 1923, **10**, 233) say that in control dogs with normal intestines the mesenteric glands contain bacteria in over 50 per cent and contain B. coli in 33 per cent of the glands examined. These facts speak conclusively for the passage of organisms from the normal bowel to the mesenteric glands. Injection of large amounts of actively growing B. coli into the normal gastro-intestinal tract of dogs was associated with the presence of B. coli or B. coli-like organism in the urinary tract in 3 of 11 dogs. It is probable that these organisms reached the urinary tract by way of the blood stream. No evidence was forthcoming that organisms reaching the mesenteric glands from the bowel tended to involve the urinary stream by way of the lymphatics. The significant of the passage of intestinal organisms through normal as well as a pathological bowel wall to the mesenteric glands cannot be overlooked. While it is undoubtedly true that these organisms reach the blood stream in but relatively small numbers and inconstantly, it is nevertheless possible that increased virulence of the organisms, lowered resistance of the host as well as actual lesions of the bowel wall would greatly increase this number of organisms reaching the blood stream.

THERAPEUTICS

UNDER THE CHARGE OF
SAMUEL W. LAMBERT, M.D.,
NEW YORK.

Principle Viewpoints on the Question of Protein Therapy.—SCHMIDT (*Therap. d. Gegenw.*, 1923, **64**, 337) gives the practical indications for protein therapy, and reminds the reader that no real difference exists between the results obtained by injections of blood, serum, vaccines, milk or tuberculin. In general the use of proteins is comparable to hydrotherapy in its non-specificity, both measures affecting the whole system in a general way. The general principles of protein therapy have been derived from empirical experience, and though various substances may apparently give the same clinical macro- and microscopical results, nevertheless the chemico-biological results may be different. He bases the indications for protein therapy on two facts: (1) Injection of protein substances causes increased bio-chemical activity of which an increase in body temperature is only one indication; (2) injection of protein substances increases the bio-chemical reactions at a point in the body where some focus of low-grade infection already exists—from which he infers that two results may follow: (1) In chronic inflammatory conditions a continuation of the inflammation may lead to a diminution of the same; or a lighting up of a chronic stationary condition may result in its complete cessation; (2) focal reactions are double phased under the action of protein substances, that is, with an increase of the inflammation, fever, etc., in the negative phase there follows a positive phase shown by the diminution of the temperature and subsidence of the inflammation, and the patient feels well during this positive phase as he felt ill during the negative phase. The particular indications for protein therapy are formulated by the author as follows: (1) Chronic, fixed and focal exogenous infections, *e. g.*, tuberculosis of bones and peritoneum; gonorrheal rheumatism and epididymitis; chronic eye, ear and joint processes; (2) chronic indolent endogenous aseptic inflammations, and abnormal metabolic conditions attending them, *e. g.*, neuralgia and arthralgia with disturbed uric acid metabolism; also constitutional diseases such as late rickets and osteomalacia. Bronchial asthma and cases of high blood-pressure are often influenced for good because of their close relation to abnormal metabolism. Combining the protein injections with other therapeutic measures may increase the effectiveness of the the latter, *e. g.*, milk injections with adrenalin in osteomalacia, neuralgia, chronic arthritis and late rickets, and with thyroid tablets in obesity; (3) chronic febrile states can often be cured as a result of the double-phased reactions of protein therapy; (4) hemorrhage. In particular milk injections have been proved to create an increased coagulating power in the blood. In severe hemorrhage (typhoid and duodenal ulcer) protein therapy is often indicated. The following technic is advised by the writer: Whole milk sterilized for ten minutes in the

water bath is used as the protein substance in this form of treatment. This combines the albumens of the milk with the dead bacteria always present, of which the streptococci and bacillus coli appear to be the principle agents in producing a reaction. The secret of the value of protein therapy lies in the focal reaction. The dose is given intramuscularly and varies between 0.5 and 5 cc. Whenever high fevers may be caused as in tuberculosis, lues, pernicious anemia, and leukemia it is wise to begin with small doses of 0.5 cc. The injections are given every two or three days and an amount used which will give a moderate general and focal reaction. The length for such a course of treatment is about four weeks.

Experiences with Atophanyl.—ZIMMERMANN (*Therap. d. Gegenw.*, 1923, **64**, 390) reports successful results in the treatment of acute rheumatism, neuralgia, and chronic rheumatism with atophanyl (E. Schering) which is a solution of the sodium salts of salicylic acid and atophan for intravenous or intramuscular injection. The ampules contain 0.5 gm. of each salt dissolved in 5 cc of liquid. This preparation can be given to patients with kidney or liver trouble without damage, but should not be used in cases of pneumonia or pericarditis. Five cc of atophanyl are given once each day for three days, and the results obtained were more satisfactory than those obtained by the use of sodium salicylate or of atophan by mouth.

The Treatment of Pyelitis.—HOHLWEG (*München. med. Wchnschr.*, 1923, **42**, 1297) concludes from his extensive experience in the treatment of pyelitis and cystitis that the most important agent is local irrigation of the bladder and kidney pelvis with 0.5 to 1 per cent solution of silver nitrate. He irrigates the kidney pelvis two to four times a week using the 0.5 per cent solution, and the 1 per cent solution for irrigation of the bladder. Because of the frequency of recurrence he considers no case cured unless the urine is bacteria-free. Instead of employing urotropin, salicylic acid and other urinary antiseptics he uses intravenous injections of 20 cc of a 0.5 per cent solution of argoflavin daily for eight to nine days. One third of the cases of pyelitis and cystitis due to the colon bacillus were cured with the intravenous injections alone. The remaining two-thirds required in addition the use of the irrigations of silver nitrate. He concludes that the ideal treatment of infections of the bladder and of the pelvis of the kidney is a combination of local irrigation with silver nitrate and intravenous injections of argoflavin.

The Rationale of Parathyroid Therapy.—VINES (*Brit. Med. Jour.*, November, 1923, p. 854) calls attention to the similarity of the signs of acute infection (fever tachycardia, sweating, shivering, increased metabolism, hyperglycemia, and loss of calcium from the body) to overaction of the thyroid gland. Overaction of the thyroid submerges the regulating action of the parathyroid as is shown by loss of calcium. Continuation of these symptoms in chronic infections leads to a pathological and new level in the sympathetic-parasympathetic balance, and an improvement in chronic infections may be obtained by restoring the normal balance by the administration of parathyroid substance or to a less degree by the administration of calcium salts.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

The Development of the Topography of the Larynx, Trachea and Lungs in the Fetus, New-born Infant and Child.—NOBACK (*Am. Jour. Dis. Child.*, 1923, **26**, 515) says that the descent of the respiratory system in relation to the vertebral column during childhood is not peculiar to that period in the development of the individual. It is merely a stage in a process in which manifestations begin in early fetal life and which continue to operate during infancy, childhood and maturity. During fetal life the topography of the epiglottis shows practically no change. It remains quite constantly opposite the first cervical vertebra. This level persists through infancy and childhood until puberty, when the adult relationship is attained so that it lies opposite the third cervical vertebra. The inferior margin of the cricoid cartilage and the lower limit of the larynx descends during the course of prenatal life from opposite the third to opposite the fourth cervical vetebra, a distance of one vertebra and one intravertebral disk. During infancy this relationship remains constant, but during later childhood another descent to the level of the sixth cervical vertebra takes place, a drop of two vertebræ and one disk. With the reaching of maturity the inferior limit of the larynx is opposite the seventh cervical vertebra. The bifurcation of the trachea undergoes a descent from opposite the third to opposite the fourth thoracic vertebra, a descent of one vertebra and one disk. This relationship is maintained during infancy, but in childhood another descent takes place, and by puberty the bifurcation is opposite an area between the fourth and fifth thoracic vertebra. This level is maintained through adult life. The apices of the lungs remain at practically the same level as the suprasternal notch throughout the course of fetal life. The upper poles of the lungs in relation to the vertebral column undergo a slight descent during prenatal life from a level opposite the seventh cervical or first thoracic vertebra to the upper margin of the second thoracic vertebra. This level is apparently maintained throughout the course of postnatal life. The inferior margin of the lungs during fetal life undergo a descent from between the ninth and tenth to opposite the tenth to twelfth veterbræ. The latter level which is present at birth, coincides quite closely to the levels given in the standard text-books for adults, thus indicating that the postnatal growth in length of the lungs is closely correlated with the increase in the length of the thorax. The lobes of the left lung in the human fetus do not vary much from the condition in the adult. The lobes of the right lung are markedly different from the lobes in the adult. The depth of the cardiac notch during prenatal life is very variable. There is a general increase in depth with increase in body length.

The Acidity of the Gastric Contents of Infants.—MARRIOTT and DAVIDSON (*Am. Jour. Dis. Child.*, 1923, **26**, 542) point out that the acidity of the gastric contents of a group of normal breast-fed infants at the height of digestion averaged PH 3.75. The acid normally present is sufficient to perform a number of important functions. Any considerable decrease in the amount of acid is likely to be associated with digestive disturbances. The acidity of the gastric contents of infants suffering from infections or nutritional disturbances is distinctly lower than that of normal infants. Sweet cow's milk, by reason of its high buffer value, is capable of neutralizing a considerable portion of the acid of the gastric juice. This is one important reason why large amounts of sweet cow's milk cannot be well tolerated by infants. Milk containing from 0.5 to 0.7 per cent of lactic acid does not neutralize the acid of the gastric contents to any greater extent than does breast milk. When such milk is fed undiluted to infants, the acidity of the gastric contents approximates that of normal breast-fed infants. It is probable for this reason that infants are able to tolerate large amounts of lactic acid milk. The observations show that the gain in weight was distinctly greater during periods of feeding when one of the lactic acid containing milks was used, than during the sweet milk periods. There was a more striking gain in weight and a lesser incidence of gastro-intestinal disturbances among this group of infants than among the sweet milk group.

Reasons for the Failure to Obtain Relief after Tonsil and Adenoid Operations.—GOLDBERGER (*Arch. Pediat.*, 1923, **40**, 767) claims that sinusitis is a disease common in children and may occur at any age. Children, whose catarrhal conditions of the upper respiratory tract do not subside after tonsillectomy and adenoidectomy, suffer in all probability from accessory nasal sinus disease. The children who are operated upon for the return of adenoid growth are probably victims of sinusitis. The antrum is the most frequently involved sinus. Two forms, the catarrhal and the purulent, are met with. Children should not be discharged as cured after upper respiratory infections such as cold, grippe, and the like, and after the acute eruptive fevers such as measles and scarlet fever particularly, until all signs pointing toward sinus involvement have subsided. Children should return at periodic intervals after operations on the upper respiratory structures to ascertain the condition of the sinuses. A hint as to the presence or the absence of sinus involvement is often obtained while the patient is under ether. Symptoms are usually constant in typical cases. Complications such as osteomyelitis, abscess of the orbit and of the brain, and meningitis are not uncommon. Diagnosis rests upon the history of previous events, roentgenograms, transillumination, and exploratory puncture. Treatment is usually conservative. Most men favor suction. Operations should be done only after all other procedures have failed.

Syphilis as a Factor in the Etiology of Mental Deficiency.—WEISS and IZGUR (*Jour. Am. Med. Assn.*, 1924, **82**, 12) tested 1794 sera from 1633 patients. Of these, 41 or 2.5 per cent were positive, and 44, or 2.7 per cent, were doubtful. If every case presenting from one

to four plus reactions on the cholesterinized antigens is considered a case of syphilis the total incidence of syphilis based on the Wassermann reaction would be 5.2 per cent. One hundred and twenty or 15.5 per cent of the patients examined clinically, presented at least one of the so-called stigmata. Of these only 13 presented more than one so-called stigma, 107 presented only one. Of those that presented only one stigma, in 85 it was unilateral or bilateral epitrochlear enlargement. In only 1 case was there the typical picture of Hutchinsonian teeth, saddle-back nose, rhagades, evidences of a past interstitial keratitis. This study was undertaken for the purpose of determing the frequency of syphilis in mental defectives. Less than 3 per cent of the defectives were syphilitic by serological test. Clinical examination revealed 15.5 per cent of the defectives with one or more of the so-called stigmata. They conclude that syphilis is uncommon in mental defectives, and that it is less common than in the general population. They question whether there is any etiological relationship whatever between syphilis and mental deficiency. They claim that if syphilis was a cause of mental deficiency, it should occur more frequently in mentally deficient children than in mentally normal children.

Diphtheria Carriers among School Population of Baltimore.—DOULL and FALES (*Am. Jour. Hyg.*, 1923, **3**, 604) made combined nose and throat cultures from 7790 children, selected at random from schools situated in the northeastern section of Baltimore. There were 409 or 5.25 per cent carriers of morphological and 136 or 1.75 per cent of virulent diphtheria carriers. The rate of carrier infection varied greatly at different seasons of the year. The incidence of carriers of virulent diphtheria organisms was 3.29 per cent in November and December and 1.49 per cent in Feburary and March, and 0.87 per cent in May and June. This variation at different seasons in carrier incidence coincides with the seasonal variation observed in diphtheria morbidity. There is a remarkable constancy at the different seasons of the year in the percentage of cultures containing morphological diphtheria bacilli which on further test were found to be virulent. These percentages were 30.45, 29.59 and 26.09 respectively in three surveys. The seasonal variation in carrier incidence was generally consistent in individual schools. The rate of carrier infection was not significantly different in the two sexes for the age period covered in this study. There was a slight but not significantly lower carrier rate among colored children than among white children. A slightly but consistently higher incidence of carrier infection was found in the younger than in the older children. Taking in consideration all of the schools surveyed, definitely but not greatly higher rates of carrier infection were found among those children who had enlarged and diseased tonsils than among those with normal tonsils. There was no noticeable difference in the carrier incidence between those having had their tonsils removed and those with normal throats. There was significant difference between those children who had histories of previous attacks of diphtheria and those with no such history in considering carrier incidence.

The Effect of Light on Organism.—CRAMER and DREW (*Brit. Jour. Exper. Path.*, 1923, **4**, 271) studied the physiological action of light on

ordinary mercury vapor bulb on the animal organism. Rats born and kept in darkness frequently show a diminution in the number of blood platelets as compared with rats kept on the same vitamin-poor diet in a well lighted room. This thrombopenia is sometimes associated with a definite anemia. Exposure of such animals to a mercury vapor lamp increases the number of blood platelets to normal, and if an anemia is present, it increases the number of red cells. Rats kept in darkness do not exhibit intestinal lesions such as are found in vitamin-A deficiency nor do they develop the bacteria infections, such as xerophthalmia, and septic lymph glands characteristic of that deficiency. They do develop these conditions sooner when placed on a deficient vitamin-A diet, than rats kept in a well-lighted room. Rats kept on a vitamin-A-free diet develop a progressive thrombopenia and atrophy of the intestinal mucosa. Exposure to a mercury vapor lamp, if applied from the beginning of the deprivation of this vitamin, delays the thrombopenia. If applied after a thrombopenia has set in, it will increase the number of platelets. Such exposures do not affect the eventual onset of the atrophy of the intestinal mucosa. Therefore it would seem that the light stimulates the formation of blood platelets. This explains the partial antagonism between vitamin-A-deficiency and exposure to light. Light is not an essential to the formation of blood platelets. In the absence of light, sufficient vitamin-A will prevent the thrombopenia.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

MAYO CLINIC, ROCHESTER, MINN.

Bismuth Salts in the Treatment of Syphilis.—Further favorable reports on the use of bismuth in the treatment of syphilis have continued to appear. KLAUDER (*Arch. Dermat. and Syph.*, 1923, **7**, 721) summarizes current observations. The dosage of bismuth preparations ranges from 0.1 to 0.2 gm., the injections being given intramuscularly every second to fourth day. Intravenous use is absolutely contraindicated. Approximately from 1 to 2.5 gm. is probably the average total tolerated dose in one month. The good effects persist for some time after the cessation of administration. Fifty per cent bismuth inunctions in human syphilis exert a feeble spirocheticidal action. So far as spirillicidal action is concerned, bismuth can be placed about midway between mercury and arsphenamine. HOPKINS (*Arch. Dermat. and Syph.*, 1923, **7**, 745) finds sodium and potassium tartrobismuthate more effective than mercury salicylate and probably approximately equal to neoarsphenamine. MCCAFFERTY (*Arch. Dermat. and Syph.*, 1923, **8**, 469), with observations on 600 injections, rates the efficiency of bismuth in primary and secondary syphilis as equal to that of arsphenamine, though slower both clinically and

serologically. He calls special attention to its efficiency in Wassermann-fast syphilis and in those who have an idiosyncrasy for arsphenamine. Stomatitis and pigmentation of the mucous membranes are negative factors in treatment, in his estimation. He noted favorable effects on the symptoms of neurosyphilis. The dosage for children is 0.01 gm. per kilogram of body weight, which is proportionately larger than for adults (Cajal and Spierer).

Treatment of Pemphigus. — The intractable character of chronic pemphigus and the usual fatal outcome make any contribution to the treatment of this disease of interest. R. H. and W. D. Davis (*Arch. Dermat. and Syph.*, 1923, **8**, 627) report a method of treatment based upon the familiar use of arsenic with the addition of coagulen. The treatment consists of intravenous injections of 1 gr. of iron cacodylate three times a week and 1.5 cc coagulen subcutaneously. The preparations may be used simultaneously or in alternation, and should be continued over a considerable period, with rest intervals of one month in every three or four. Of 7 cases reported as treated by this method, 1 recovered completely after eleven months; 2 recovered in from three to six weeks; 1 patient was almost well; 1 improving, and there had been 1 death up to the time of reporting. The treatment seemed to be the most effective in acute rapidly progressive cases. In the discussion which followed the presentation of this paper, and in the paper itself, attention was called to the remissions well known to occur in pemphigus, some of which may be very prolonged and give the impression of cure. Ormsby gave it, as his belief, that pemphigus is always fatal, although some cases run a protracted course. He alluded to the value of blood transfusions in occasional instances, reporting 1 case in which six were given, with remarkable improvement. On the other hand, Schamberg has seen no favorable effects from this procedure. The general trend of the discussion certainly indicated the profound uncertainty surrounding the treatment of this disease and the fact that even apparent clinical cures do not necessarily mean a permanent result. Any method of treatment, however, deserves consideration and trial under the circumstances.

Thymus Irradiation in Psoriatics.—Gawalowski (*Acta dermat.-ven.*, 1923, **4**, 105) discusses his experience with the irradiation of the thymus gland in adults for the treatment of psoriasis. The rationale of the procedure is based on Samberger's and Brock's observations, which led them to maintain that psoriasis is a disorder of keratization which is controllable to some extent through the hormone of the thymus gland. The author discusses in some detail the roentgenological technic of reaching the glandular tissue behind the sternum, since much depends upon accuracy of dosage. In 82 treated cases, 17 per cent were cleared up, 48.8 per cent improved, no results were obtained in 6.1 per cent, 2.4 per cent were made worse and 25.7 per cent disappeared from observation. This gives 65.8 per cent benefited, as compared with Brock's 66 per cent. The dosage employed was higher than Brock's, and only two treatments were required to produce the best results. The interval between treatments was six weeks. The 9 patients who were made worse or received no benefit were later

cleared up with Byla's "thymosine." Twenty non-psoriatics were likewise treated. Pigmentary disturbance in 1 case, marked sweating, increased capillary irritability and marked itching were occasionally noted. The results in psoriasis justify the method in the author's opinion.

Arsenical Melanosis and Argyria of the Skin and Mucous Membranes after Silver and Neoarsphenamine.—Kogoj (*Acta dermat.-ven.*, 1923, **4**, 94) describes what appears to be the first authentic instance of argyria following the use of silver arsphenamine. The patient was a young woman, who, after twelve injections of silver arsphenamine and twelve injections of neoarsphenamine, developed a dirty-gray pigmentation of the entire skin and all visible mucous membranes. The author studied elaborately the various differential possibilities and the histological characteristics of the lesion, reaching the conclusion that the pigmentation combined the known characteristics of arsenic and silver pigmentations of the skin. The literature of the various pigmentary disturbances, including melanoses ascribable to the arsphenamine, is elaborately cited, with a bibliography of sixty-eight titles.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

An Unusual Accident during Delivery at Term.—Martin and Brinkley (*Virginia Med. Month.*, October, 1923, p. 457) describe the case of a multipara in labor supposed to have the child in breech presentation. Labor proceeded slowly and the physician returned some hours after making an examination intending to give chloroform and deliver the child. On a second examination, the face presentation was recognized. When the cervix was fully dilated the patient was given chloroform and pituitrin; this was followed by a very severe uterine contraction with several slight pains during the next thirty or forty minutes. There was a moderate flow of dark blood from the vagina. The head did not descend and the physician prepared to perform version. On introducing his hand it entered the abdomen; version was quickly performed and a dead child delivered. The placenta was readily removed. On further examination the vaginal vault was almost completely torn away from the cervix and packing of sterile gauze was introduced and the patient sent to a hospital. Under anesthesia the abdomen was opened, when it was found that the uterus had been torn away from its vaginal attachments almost completely. The broad ligaments were lacerated almost up to the pelvic brim on either side. On the right side the tear extended through the vaginal wall practically to the vulva. The uterus, left

tube and ovary were removed. The torn fascias were brought together, the vessels tied and a drain inserted. The patient made a somewhat tedious recovery. There was drainage through the vagina and some sloughing tissue came away. About a month after operation the patient left the hospital and was found, when examined subsequently, to be in good condition. The combination of chloroform and pituitrin seems an unusual one. Apparently the purpose was to remove pain and stimulate uterine contraction. The result was what may be expected in cases of abnormal presentations and complicated labor, when pituitrin is given. No more dangerous procedure could be employed.

Liniæ Albicantes in Varying Degree in Pregnancy.—KERMAUNER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, **64**, 125) calls attention to the fact that the occurrence of this phenomenon in pregnancy has been supposed to be of a purely physical nature. Sellheim has called attention to this occurrence as a biological element. The writer has studied the subject from this point. It has commonly been supposed that this evidence of distention of the skin of the abdomen is most marked in young primiparæ indicating the increased tension upon the tissues. This, the writer does not accept. He believes that peculiarities in the shape of the mother's body predispose to this occurrence. He has found this distention of the skin most abundant on the abdomen beneath the umbilicus, extending to the pubes, on the inner aspect of the thighs, the outer portion of the hips extending to the mid-line in cases where the entire abdominal wall has been firm, smooth and moderately fat. Where the tissues were relaxed, this condition developed a hand's breadth above the umbilicus and but little in the region of the hips. In some cases this was seen four fingers' breadth above the pubes, extending across the abdomen, the remainder of the abdomen remaining free. At other times the upper portion of the thighs and hips, and even the back showed this condition. The writer believes that edema of the skin has nothing to do with the formation of these so-called "stripes." Furthermore, he does not consider that distention alone of the tissues accounts for their occurrence. He has seen a similar condition in the bodies of men where the abdomen has grown fat very rapidly. He has never seen it where ascites or tumor was present. He is convinced that the occurrence of this phenomenon depends upon conditions in the connective tissue in the deep fat of the abdominal wall. Pregnancy, naturally, supplies the conditions favorable for increased nutrition and for increased contraction and relaxation of abdominal muscles. That it is not the pressure of the enlarged uterus is shown from the fact that in early pregnancy, when the uterus is still deep in the pelvis, patients complain of increased pressure and a sensation of weight in the abdominal walls. Multiparæ often feel this more acutely than primiparæ. Distention of the bowel may have something to do with this, but the increased deposit of fat, called by Bauer "lipophilie," is the essential element. In cases where this process goes on in the breasts the stripes may also develop. The writer cites the case of a young woman, aged twenty years, who became fat very suddenly. In six months the condition had increased so greatly that ascites and edema were present and the

appearance of the patient, when compared with a photograph taken four years previously, would not have permitted her recognition as the same person. These stripes appeared over the whole body with the exception of the face. One may the better understand this condition by considering the connective tissue of the skin as divided into practically two layers, one of which is superficial, the other deeper. It is in the deeper layer that this phenomenon develops. The writer considers the condition known as dystrophia adiposogenitalis, as allied to that under discussion. A lack of function in the pituitary body is thought to be the cause, and if this persists after delivery the abdominal fat condition may greatly impair the appearance of the patient. One occasionally sees cases in which the elasticity of the skin is excessive. In these patients the eyelids, the tissues about the neck and about the ears may hang in folds. Very badly nourished children may also show these symptoms. In multiparous women, whose tissues are greatly relaxed and wasted the same is seen. Myxedema must not be confused with this condition. In myxedema there are no stripes formed, and the administration of glandular extracts clears up the condition. It can also be differentiated from edema of the skin. It cannot be overlooked that in pregnancy all tissues become unusually elastic and lose their tone readily. To this is added disturbances of function in secretory glands, and when these conditions are considered it is not strange that such phenomena should appear.

OPHTHALMOLOGY

UNDER THE CHARGE OF

EDWARD JACKSON, A.M., M.D.,

DENVER, COLORADO,

AND

T. B. SCHNEIDEMAN, A.M., M.D.,

PHILADELPHIA.

The Toxic Action of Tobacco and Alcohol upon the Eye.—SATTLER (*Klin. Monatsbl. f. Augen*, 1922, **60**, 526) reports that visual disturbances from tobacco and alcohol have increased six-fold at the Konigsberg University Eye Clinic from 1913 to 1921. Inquiry as to the cause of such increase among 47 patients showed that about one-half had been smoking or chewing not ordinary tobacco, but self-grown, simply dried; the latter contains about twice the amount of nicotine as the properly prepared tobacco of commerce; chemical examination showed, moreover, that whereas only 15 per cent of nicotine went over in commercial tobacco, 27 per cent did so in the simply dried form. A coöperating cause is unhygienic way of smoking: short dirty pipes, inhalation of the smoke into the lungs. The fact that over one-third of the patients were imbibers of distilled spirits (0.1 to 0.25 liter daily) makes it prob-

able that the methyl alcohol content of 2 per cent contained therein exerted a toxic effect upon the eye; each daily dose of 0.5 liter contains 10 gm. of methyl alcohol (minimum toxic dose for the eye $\frac{8}{2^{0}}$ gr.) which in consequence of protracted oxidation and excretion (methyl alcohol three to five days, ethyl alcohol only twenty hours) may exert a deleterious effect upon the eye through cumulative effect. Under-nourishment is a predisposing cause of lessened resistance to poisons. Examination of the visual field for white and colors showed in 21 cases different zones of saturation of the so-called central scotoma; the point of greatest saturation in about one-half the cases did not involve the point of fixation, but a region between this and the blind spot, generally in the mid-point, but occasionally nearer one or the other extremity; in the remaining half of the cases saturation was limited to the point of fixation; in 3 cases the scotoma lay above or below this point; in none did the defect extend into the periphery. During convalescence the scotoma gradually receded to the point of fixation or to the blind spot; a larger scotoma for red in 2 cases vanished before that for blue; all the cases were recent. The above clinical determinations of the scotomata so variable in form, extent and density are explicable by the anatomical findings of the variable areas of degeneration observed to occur in the optic nerve.

Glaucoma and Syphilis.—CARLOTTI (*Clin. Ophthal.*, 1923, **12**, 428) observes that the role played by syphilis in the causation of the different forms of glaucoma has been noted by a number of authors. It is, however, remarkable that in the some 50 publications devoted annually to glaucoma, lues and its therapeutic indications plays so little a role. Thus Elliott in his very complete review, does not allude to syphilis. Gama Pinto in his article for the Encyclopedia remarks "that syphilis has been mentioned among the causes of glaucoma; Connor, Rechey, Pflueger and Samelsohn claim to have observed cases of glaucoma which were not cured by surgical intervention but yielded to antisyphilitic treatment. Morax also admits that glaucoma may be a secondary consequence of specific disease." The author reports 26 cases of glaucoma which go to prove that treponemic infection may give rise to all varieties of glaucoma, and that such ocular localization is subject to the same rules from the therapeutic point of view as other manifestations of syphilis. Medical treatment should be prompt and prudent; in two of the cases cited, injections of cyanide were followed by apparent aggravation. When the glaucomatous lesions are advanced, surgery takes the place of medical therapeutics.

Final Results of Sclerecto-iridectomy in the Treatment of Chronic Glaucoma.—LAGRANGE and BARON (*Arch. d'opht.*, 1923, **40**, 15), the former of whom introduced subconjunctival scleral resection in 1905 for the purpose of effecting permanent fistulization, sum up results obtained by this method, in 49 patients operated upon between 1912 and 1921 and followed from one to ten years; the results show that operative success was maintained in 82 per cent of the cases, as regards visual acuity, if the development of senile cataract subsequently is disregarded, and 73.1 per cent if the latter is considered a cause of impaired vision. The same series shows that the intraocular tension remained normal

in 8 per cent, and if hypotonia can be regarded as favorable, in 87.5 per cent. There was never any infection, primary or secondary, since the scleral orifice was recovered by a thick layer of mucous membrane; neither was there hypotonia from wounding of the ciliary body because the excision is purely scleral, about 3 mm. in length, and does not exceed 0.8 mm. in width and, consequently, cannot touch the ciliary body. The writers finally insist that sclerecto-iridectomy is the operation for chronic glaucoma and not for the acute disease; after so many repetitions of this limitation, they profess astonishment that some operators fail to reserve the fistulizing method of the Bordeaux School for chronic glaucoma and for it alone.

Diseases of the Optic Nerve in Cerebral Syphilis.—ELEONSKAJA (*Russk. Opht. Jour.*, 1922, **1**, 280) found in 100 cases of choked disc cerebral syphilis as the cause in 33 (12 females and 21 males); in 26 of these the nerve affection was bilateral and in 3 monolateral. In 3 cases which came to section, gumma of the brain was found; in 2 hydrocephalus internus; in 1 congenital lues. Of the remainder observed during life alone, in 8 there were indications of basilar meningitis, in 10 no definite localization and in 8 no objective signs whatever on the part of the central nervous system. As regards the remaining cerebral nerves, there was present in 9 oculo-motor paresis, in 7 abducens paresis, in 1 facial hemianesthesia, in 1 disturbances of smell and hearing, and in 1 paresis of the facial. Under specific, usually combined, treatment in the majority of cases there was improvement in the appearances of the papilla; the visual acuity improved, however, in cases only where treatment had been begun sufficiently early. Neuritis of the optic nerve was observed in cerebral syphilis only 8 times (6 males and 2 females), of which 5 were bilateral, 2 monolateral and 1 in combination with choked disc of the opposite side. Disturbances of vision were absent in 2 of the cases, in 2 there was complete blindness, in 2 vision equalled $\frac{1}{10}$ and in 2 the determination of the visual acuity was impossible on account of the severity of the general disease. In 2 the inflammation of the nerve began in the course of the first year following infection, in the remaining 6 cases in three, six and twelve years respectively after infection. All the cases presented grave involvement of the central nervous sytem (cephalalgia, confusion, vomiting, palsies of the extremities, cerebral nerves, etc.). Specific treatment caused improvement in the general condition in all of the cases. But the visual acuity became normal in 2 only, the remainder eventuated in more or less marked optic atrophy with corresponding diminution of the visual acuity (0.1 and worse).

The "Laughing" Sign Shortly after the Extraction of Cataract.—CHARLIN (*Annal. d'ocul.*, 1923, **16**, 629) remarks that extraction of the lens, even under the best conditions, is a procedure subject to numerous accidents the results of which are always problematical for the success of the operation; it is difficult without ophthalmoscopical examination to arrive at a prognosis with any degree of certainty. Such an examination cannot be made before the expiration of a week, for the reason that it is not prudent to undertake a prolonged investigation before the formation of a firm corneal cicatrix. There is, however, a sign easily and rapidly obtained which assures a quite satisfactory prognosis at

the first change of the bandage, twenty-four to forty-eight hours after operation. It is made as follows: The patient is requested to look at the surgeon's face; the vision will be very confused; if now a strong convex lens, say +13 D, is held before the eye, the patient immediately receives a quite sharp image upon his retina; this pleasant surprise is so unexpected that he is unable to restrain a burst of laughter; this reflex laugh indicates a healthy condition of the deeper membranes. Temporary opacities of the media, such as intraocular hemorrhages and masses of cortex in the pupil, may interfere with the formation of an image and the interposition of the lens will produce no improvement in the vision; such a negative result has, however, only a limited value. Reflex outbreak of laughter is a favorable early postoperative indication of the success of the operation.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Disposition of Ureters in Renal Tuberculosis.—When a nephrectomy is performed for renal tuberculosis what should be done to the ureter? This question has been asked by many surgeons for many years and many answers have been forthcoming, usually based upon personal opinion rather than on careful follow-up studies. It will be of interest, therefore, to consider a report of WALTERS (*Minn. Med.*, 1923, **6**, 307), of the Mayo Clinic, based upon replies received from 282 patients operated upon between 1915 and 1920. Ligation of the ureter with catgut and sterilization of the cut end with the cautery seems to have been the most effective means of treating the tuberculous ureters that were not sufficiently strictured to produce distention. In 48 per cent of these cases there was primary union of the incision before the patient was dismissed from observation and the incisions remained healed without subsequent drainage. Twenty-seven per cent of the patients similarly treated and whose incisions were draining when they were dismissed (from three to five weeks after operation) report subsequent permanent healing of their wounds. As might be expected, one of the least effective methods of treating the tuberculous ureter from the standpoint of wound-healing is sealing the cut end of the ureter for from forty-eight to seventy-two hours by leaving two pairs of forceps on the renal pedicle, which is too short to be ligated accurately and securely. This method was necessary in 28 cases. In 13 other cases the incision healed after the patients had been

dismissed from observation. Suturing the cut end of the ureter to the margin of the skin at the lower angle of the wound, which allows the escape of the contents of the ureter to the outside without contamination of the wound, has been practically discarded since only 18 per cent of such cases had primary union of the wound, although an additional 53 per cent healed subsequently. The results of partial or complete ureterectomy with nephrectomy, as measured by wound-healing and end-results in 14 cases with stricture of the tuberculous ureter insufficient to produce obstruction and distention, do not warrant the routine employment of the procedure. The cases of demonstrable strictured and distended tuberculous ureters obviously form a separate group, since the stricture forms a closed sac if it is distal to the cut end of the ureter. However, this uncommon condition was found in only 3 per cent of the cases. The whole ureter should be removed with the kidney if the strictured ureter is distended to a point below the stricture. In the other cases the ureter should be clamped with a hemostat without separating it from its fatty sheath, in order not to disturb its circumureteral circulation, then divided with the cautery and dropped back without a ligature, which might act as a foreign body. After thorough hemostasis the wound is closed without drainage.

Uterine Suspension.—Some operations are invented, run a longer or shorter period of popularity and then pass into obscurity. Occasionally one of these procedures is revived by a well-known surgeon with the belief that the operation has not received its just due, and he undertakes to be its champion. Apparently such is the case with the Olshausen operation for uterine suspension, which has been brought from its dusty shelf by GRAVES (*Am. Jour. Obst. and Gynec.*, 1923, **6**, 137), for reasons which we shall later set forth. His particular method of performing the operation consists of grasping the round ligaments by half-length clamps at points usually about ½ inch from the attachment of the ligament to the horn of the uterus. The clamps are locked somewhat tightly in order deliberately to traumatize the peritoneal covering at those points. The uterus being brought up to the abdominal wound by traction on the clamps, beginning on the right a suture of No. 7 braided silk, doubled, is passed beneath the round ligament at the point grasped by the half-length clamp. It is then passed into the abdominal wall at a chosen level, about 1½ inches from the edge of the wound, through the peritoneum, rectus muscle and fascia. At a point about ½ inch from its exit in the fascia the suture is then carried back into the peritoneal cavity through the same layers in reverse order. While the assistant approximates the ligament to the abdominal wall by traction on the clamp, the operator draws the suture snug, removes the clamp on the ligament and clamps the suture ends without tying the knot. The same procedure is then carried out on the left side and both knots tied inside the peritoneal cavity, that on the right being tied last. The tying of the knots is very important as they should be drawn as tightly as possible. Concerning the advantages of the operation, the author states that in the first place it permanently overcomes the cardinal lesion of descensus, and does so on sound mechanical principles. Moreover by creating purely

artificial ligaments the restoration of the uterus is attained entirely independently of the natural ligaments. The attempt to redisintegrate ligaments which have already proved themselves treacherous seems illogical to the author. In this operation a better result may be attained by the simple passing of two sutures than can be accomplished by the most laborious individual reconstruction of all the ligamentary supports of the uterus. In addition the operation offers the widest latitude in repairing varying degrees of descensus or length of uterine body. Thus the greater the amount of descensus the higher may the attachment be made on the anterior abdominal wall, even to a point half-way to the umbilicus. If the descensus is so great that the uterus can be drawn completely outside the abdominal wound, the fundus may be amputated, the round and broad ligaments attached to the cervical stump and the Olshausen operation performed in the usual way. If the uterine segment is too short, as may happen in fat women with atrophied genitals, or if extra mobility is desired, as in young women with simple retroversion, the ligaments may be attached at greater distances from the uterus. Thus, no matter what condition presents, the desired position of the uterus may be gauged with the greatest accuracy. The author has performed this operation 1370 times, 50.2 per cent of the cases being for general prolapse of all stages. He has been able to obtain follow-up examinations on 746 cases at periods ranging from two months to eight years after operation. In 6 cases the attachment failed to hold. In 15 cases of the entire series one of the silk stitches became infected and in 6 of these the stitch required removal; in the remaining cases the wound healed or the stitch was discharged spontaneously. There were no known cases of intestinal obstruction, nor of dystocia following the operation, although in 1 case a small hernia worked its way through the site of the silk ligature on one side of the wound.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

The Life Cycle of Bacillus Fusiformis.—The question whether fusiform bacilli and the spirilla with which they are practically always associated in normal, as well as in pathological condition, are separate organisms or parts of the life cycle of one, has long been a subject for discussion. TUNNICLIFF (*Jour. Infect. Dis.*, 1923, **33**, 147) studied a pure culture of Bacillus fusiformis isolated from a normal tonsil. The

material was grown anaërobically for four days in ascites broth and then subcultures were made on goat blood agar slants. The culture was repeatedly plated out on blood and ascites agar, and the colonies were well separated in ascites agar with and without fresh kidney tissue to insure a pure culture. It was found that the organism was an obligate anaërobe, growing at 36° C., but not at room temperature. A slightly offensive odor emanated from successful cultures. The bacillus was extremely pleomorphic, forming straight and wavy, non-motile threads of various lengths, the bacilli and filaments staining blue with Giemsa stain, and bodies within the organisms bright pink. Under certain conditions these bodies appeared to fall out of the threads and developed into motile spirilla with from 1 to 10 curves. More frequently the spirilla developed from the bodies in the interior of the cell and later emerged from the end of the thread, or the filament ruptured, liberating them. The spirilla then seemed to degenerate, and by Giemsa stain, showed inside and out elongated, slightly pointed blue bodies containing deeply staining granules at their ends, resembling short fusiform bacilli, seen in early cultures. The spirillar and bacillary cycles appeared to be connected also by a symplastic stage, when a mass of bodies was formed due to changes in the organisms, from which bacilli and threads emerged. The authoress concludes by stating that "these observations tend to confirm the theory that fusiform bacilli and spirilla are different forms in the life cycle of one organism."

Studies of Fusiform Bacilli and Spirochetes. Occurrence in Tonsils and Adenoids.—Fusiform bacilli and spirochetes in connection with actinomyces-like granules of the tonsils having been noted by Davis (*Jour. Infect. Dis.*, 1914, **14**, 144) and later, in another series by Pilot and Davis (*Ibid.*, 1918, **23**, 231) in 25 per cent of extirpated tonsils, Pilot and Brams (*Ibid.*, 1923, **33**, 134) undertook to determine the frequency of these bacteria in excised tonsils and adenoids. Accordingly, the tonsils of 100 children and the adenoids from 46 of the same children were studied. Actinomyces-like granules were found in 19 per cent of the tonsils, but in only one mass of adenoid tissue, such a low incidence in the latter being attributed by the authors to the nature of the structure of the adenoids, with its folds hanging free in the nasopharyngeal vault, permitting of excellent drainage. Tonsillar smears and cultures were made from the bottoms and sides of the crypts. In the actinomyces-like granules, filaments, short fusiform bodies, typical fusiform bacilli, spirochetes and Gram-positive cocci comprised a constant, striking characteristic of these masses, illustrating a remarkable symbiotic relationship. Cultures were made by inoculating blood-agar slants. Fusiform bacilli were found in 82 per cent of the extirpated tonsils and in 32.6 per cent of the adenoids. Spirochetes appeared in 25 per cent of the tonsils, particularly in the actinomyces-like granules, and in 4.34 per cent of the adenoids. Associated with them in both tonsils and adenoids were streptococci of the hemolytic and viridans types and other bacteria. In morphology, the fusiform bacilli and spirochetes resembled those encountered about teeth and in certain putrid and gangrenous processes of the mouth and respiratory tract. The authors conclude by saying that "the tonsils and adenoids may be important sources of infections with these organisms and associated bacteria."

Studies in Fusiform Bacilli and Spirochetes. Occurrence in Otitis Media Chronica.—In a study of chronic middle-ear discharges, PILOT and PEARLMAN (*Jour. Infect. Dis.*, 1923, **33**, 139) found fusiform bacilli usually together with spirochetes in 15 instances, in greatest numbers in the intensely fetid, purulent secretions. In the less offensive discharges, they were fewer, while in 3 cases in which the odor was distinctly foul, these organisms could not be demonstrated. Twelve cases, having chronic non-fetid discharges, did not reveal them and they were not encountered in cases of acute otitis media. The technic consisted of direct smear preparations, stained with 10 per cent carbol fuchsin, or gentian violet or by the Fontana method. The fusiform bacilli varied in length from 5 to 12 microns and tended to be Gram-positive. Cultures were obtained under anaërobic conditions in 2 instances. On smear, the spirochetes were not as numerous as the bacilli, being absent in 3 cases where the bacilli were present. Varying considerably in form, some exhibited 2 to 5 turns, others 5 to 15. In morphology both the bacilli and spirochetes resembled those found in Vincent's angina, pulmonary gangrene, and about normal teeth and tonsils. The authors believe that the pathway of infection is along the Eustachian tube from the naso-oro-pharynx, as these organisms could not be demonstrated in the normal canal; and that the ordinary pyogenic bacteria prepare the soil for the anaërobes, inasmuch as the bacilli and spirochetes were never found in pure form.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Housing and Health.—WALKER (*Am. Jour. Pub. Health*, 1923, **13**, 897) studied the relation between our health and our environment based upon the prevalence of disease in the city of Detroit with special reference to the influence of the type and sanitation of dwellings upon disease. In the early part of the present century, the author states, we passed through a period when many ills were attributed to housing. Plumbing codes were written with great rigidity. Diphtheria and scarlet fever were attributed to leaky and defective plumbing which permitted sewer air and gas to escape into the room. Lack of ventilation and foul odors were blamed for tuberculosis and malaria. With the greater knowledge of the germ theory of disease and the modes of transmission, the pendulum swung to the other extreme when direct

contact, or at least very close contact, was held to be of prime importance in disease transmission and prevalence. The time is now at hand for the proper correlation of these factors relative to housing. The data presented indicate quite clearly for the period covered a relationship between sanitary environment and infant mortality, tuberculosis and pneumonia, which should not be considered lightly. Secondly, the relation of light to the development of rickets and the general welfare of child-life has become an established fact. The results of this study should be sufficient to stimulate interest in the improvement of housing conditions, and the formulation of housing codes, which will insure the lighting of all rooms used for habitation to an extent equal at least to 0.5 of 1 per cent of the outside light intensity.

Vaccination Technic and Certification.—GRUBBS (*Pub. Health Reports*, 1923, **38**, 2201) discusses vaccination from the standpoint of the maritime quaratine officer especially and describes the procedure in use at the New York Quarantine Station. The reactions of immunity are described briefly and the point is brought out that as soon as one of these reactions enables one to judge of the immunity of the individual the person may be released; in other words, vaccination is used not only "to produce immunity but also to measure it." The following are the conclusions: (1) By making use of the reactions that follow vaccination, it is possible to eliminate much of the delay now considered necessary to prevent the spread of smallpox; (2) in order to encourage vaccination, these reactions should be observed and records should be furnished the individual as a proof of his immunity; (3) a person certified as immune to smallpox should not be detained by any smallpox quarantine.

Results of a Three-year Trachoma Campaign Begun in Knott County, Kentucky, in 1913.—MCMULLEN (*Pub. Health Reports*, 1923, **38**, 2463) states that in 1912, among 4000 persons examined, 500 or 12½ per cent had trachoma. As a result of surgical treatment the disease has been practically eradicated. A survey recently shows that the treatment had been permanently successful in the great majority of cases, and that in about ten years the disease had been practically eliminated in a badly infected region.

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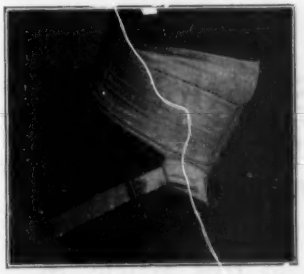

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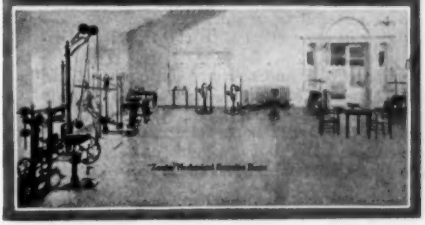

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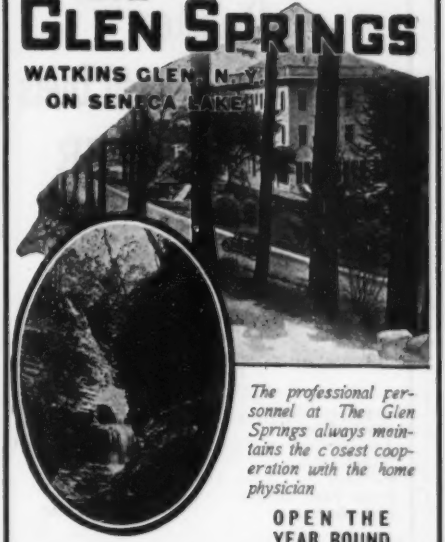

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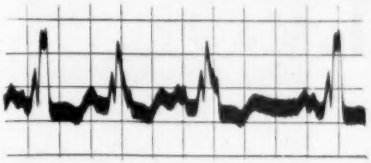

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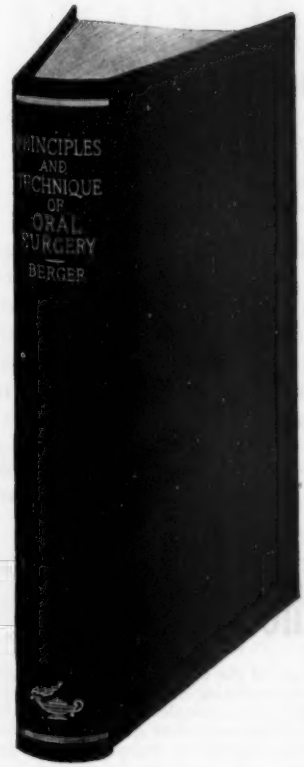

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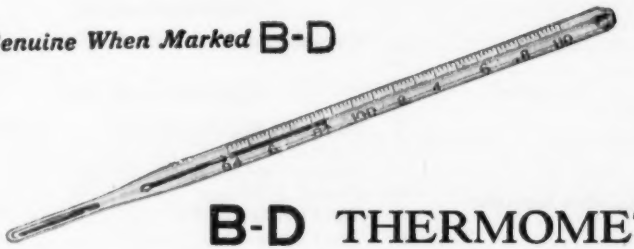

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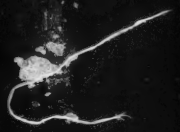

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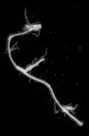
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